TOXICOLOGICAL REVIEW

of

BARIUM AND COMPOUNDS

(CAS No. 7440-39-3)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

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FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard identification and dose-response information in IRIS pertaining to chronic exposure to barium. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of barium and compounds.

In Section 6, EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose-response (U.S. EPA, 1995a). Matters considered in this characterization include knowledge gaps, uncertainties, quality of data, and scientific controversies. This characterization is presented in an effort to make apparent the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this review or other questions relating to IRIS, the reader is referred to EPA's Risk Information Hotline at 513-569-7254.

AUTHORS, CONTRIBUTORS, AND REVIEWERS

Chemical Manager/Author

Harlal Choudhury, D.V.M., Ph.D., D.A.B.T.
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

Contributing Authors

Joan Colman, Ph.D. (RfD Assessment)
Senior Scientist
Syracuse Research Corporation
Syracuse, NY

Lisa Ingerman, Ph.D. (RfC, RfD, and Cancer Assessments)
Senior Scientist
Syracuse Research Corporation
Portland, OR

Phillip Robbins, M.S.
Scientist
Syracuse Research Corporation
Cincinnati, OH

Reviewers

This document and summary information on IRIS have received peer review both by EPA scientists and by independent scientists external to EPA. Subsequent to external review and incorporation of comments, this assessment has undergone an Agencywide review process whereby the IRIS Program Manager has achieved a consensus approval among the Office of Research and Development; Office of Air and Radiation; Office of Prevention, Pesticides, and Toxic Substances; Office of Solid Waste and Emergency Response; Office of Water; Office of Policy, Planning, and Evaluation; and the Regional Offices.

AUTHORS, CONTRIBUTORS, AND REVIEWERS (continued)

Internal EPA Reviewers

Edward Ohanian, Ph.D.
Senior Health Scientist
Health and Ecological Criteria Division
Office of Water
U.S. Environmental Protection Agency
Washington, DC

Yin-Tak Woo, Ph.D.
Director, Risk Assessment Division
Office of Prevention, Pesticides, and Toxic Substances
U.S. Environmental Protection Agency
Washington, DC

External Peer Reviewers

Marvin Goldman, Ph.D.
University of California, Davis
Davis, CA

Arthur Gregory, Ph.D.
Techto Enterprises
Luray, VA

Paul Mushak
PB Associates
Durham, NC

Summaries of the external peer reviewers' comments and the disposition of their recommendations are in Appendix A.

1. INTRODUCTION

This document presents the derivation of the noncancer dose-response assessments for oral exposure (the oral reference dose, or RfD), and inhalation exposure (the inhalation reference concentration, or RfC) and the cancer hazard and dose-response assessments for barium (Ba).

The RfD and RfC are meant to provide information on long-term toxic effects other than carcinogenicity. The RfD is based on the assumption that thresholds exist for certain toxic effects, such as cellular necrosis, but may not exist for other toxic effects, such as some carcinogenic responses. The RfD is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime. The inhalation RfC is analogous to the oral RfD. The inhalation RfC considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects). It is expressed in units of mg/m^3.

The carcinogenicity assessment is meant to provide information on three aspects of the carcinogenic risk assessment for the agent in question: the EPA classification and quantitative estimates of risk from oral exposure and inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which any carcinogenic effects may be expressed. Quantitative risk estimates are presented in three ways. The *slope factor* is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg-day. The *unit risk* is the quantitative estimate in terms of either risk per µg/L drinking water or risk per $\mu g/m^3$ air breathed. The third form in which risk is presented is a drinking water or air concentration, providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

Development of these hazard identification and dose-response assessments for barium has followed the general guidelines for risk assessments as set forth by the National Research Council (NRC, 1983). EPA guidelines that were used in the development of this assessment may include the following: Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a), Guidelines for the Health Risk Assessment of Chemical Mixtures (U.S. EPA, 1986b), Guidelines for Mutagenicity Risk Assessment (U.S. EPA, 1986c), Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a), Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991), Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996b), Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity (U.S. EPA, 1994a), Proposed Guidelines for Neurotoxicity Risk Assessment (U.S. EPA, 1995b), Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA, 1994b), Recommendations for and Documentation of Biological Values for Use in Risk Assessment (U.S. EPA, 1988), Use of Benchmark Dose Approach in Health Risk Assessment (U.S. EPA, 1995c), and Guidance on Risk Characterization (U.S. EPA, 1995a).

The literature search strategies employed for this compound were based on the Chemical Abstracts Service Registry Number (CASRN) and at least one common name. As a minimum, the following databases were searched: RTECS, HSDB, TSCATS, CCRIS, GENETOX, EMIC, EMICBACK, ETICBACK, TOXLINE, CANCERLINE, MEDLINE, and MEDLINE backfiles. Any pertinent scientific information submitted by the public to the IRIS Submission Desk also was considered in the development of this document.

2. CHEMICAL AND PHYSICAL INFORMATION RELEVANT TO ASSESSMENTS

Barium is a dense alkaline earth metal in Group IIA of the periodic table. The free element is a silver-white soft metal that oxidizes readily in moist air and reacts with water. Barium does not exist in nature in the elemental form but occurs as the divalent cation in combination with other elements (ATSDR, 1992). The physical and chemical properties of barium and selected barium compounds are presented in Table 1.

Barium makes up 0.05% of the earth's crust, and the two most prevalent naturally occurring barium compounds are barite (barium sulfate) and witherite (barium carbonate) ores. Barium enters the environment through the weathering of rocks and minerals and through anthropogenic releases. The primary source of barium in the atmosphere is industrial emissions (ATSDR, 1992). Barium concentrations ranging from 2×10^{-4} to 2.8×10^{-2} µg/m^3 (mean of 1.2×10^{-2} µg/m^3) have been detected in urban areas of North America (ATSDR, 1992). Barium is naturally occurring in most surface waters and in public drinking water supplies. Barium content in U.S. drinking water supplies ranges from 1 to 20 µg/L; in some areas barium concentrations as high as 10,000 µg/L have been detected (WHO, 1990). Barium is ubiquitous in soils, with concentrations ranging from 15 to 3,000 ppm (ATSDR, 1992). Barium is also found in many foods. In most foods, the barium content is relatively low (< 3 mg/100 g) except for Brazil nuts, which have a very high barium content (150-300 mg/100 g) (WHO, 1990).

The primary route of exposure to barium appears to be ingestion in drinking water and food. A daily intake of 0.03-0.60 µg Ba/kg-day from drinking water can be estimated using the drinking water concentration of 1-20 µg/L, a reference consumption rate of 2 L/day, and body weight of 70 kg. The World Health Organization (WHO) (1990) reported several published estimates of dietary intake of barium by humans; daily dietary intake ranged from 300 to 1,770 µg Ba/day, with wide variations; this is equivalent to 4-25 µg Ba/kg-day, assuming a 70 kg adult body weight. The range from these two sources combined is 0.004-0.026 mg Ba/kg-day.

Table 1. Physical and chemical properties of barium and selected barium compounds

	Barium	Barium acetate	Barium carbonate	Barium chloride	Barium hydroxide	Barium oxide	Barium sulfate
CAS Registry number	7440-39-3	543-80-6	513-77-9	10361-37-2	17194-00-2	1304-28-5	7727-43-7
Molecular formula	Ba	$Ba(C_2H_3O_2)_2$	$BaCO_3$	$BaCl_2$	$Ba(OH)_2$	BaO	$BaSO_4$
Molecular weight	137.3	255.45	197.37	208.27	171.38	153.36	233.4
Melting point, °C	710	41	1,740	960	408	1,920	1,580
Boiling point, °C	1,600	no data	decomposes at 1,300	1,560	760	2,000	1,149
Vapor pressure, mm Hg	10 at 1,049°C	no data	essentially zero	essentially zero	no data	essentially zero	no data
Water solubility, g/L	decomposes	588 at 0°C, 750 at 100°C	0.020 at 20°C	375 at 20°C	16.7 at 0°C	1,500 at 0°C	0.00115 at 0°C
Specific gravity	3.5 at 20°C	2.02 below 24.7°C	4.43	3.1	2.18 at 16°C	5.72	4.58

Source: ATSDR, 1992.

3. TOXICOKINETICS RELEVANT TO ASSESSMENTS

3.1. ABSORPTION

3.1.1. Gastrointestinal Absorption

Data on gastrointestinal absorption of barium in humans are limited to a study conducted by Lisk et al. (1988). In this mass balance study of one man consuming a single dose of 179.2 mg barium in 92 g of Brazil nuts, it was estimated that at least 91% of the dose was absorbed.

A wide range of absorption efficiencies has been reported in animal studies. In some animal studies, gastrointestinal absorption was reported to be < 11% (Cuddihy and Griffith, 1972; Cuddihy and Ozog, 1973; Della Rosa et al., 1967; Taylor et al., 1962). Some of these studies may have been terminated prior to completion of absorption (Cuddihy and Ozog, 1973; Taylor et al., 1962). Other studies reported relatively high (30%-85%) gastrointestinal absorption of barium (Richmond et al., 1960, 1962a, 1962b; Richmond and Furchner, 1970; Taylor et al., 1962). However, most studies determined absorption by addition of body burden to total urinary excretion, after removal of the gastrointestinal tract. This method does not account for barium absorbed and then excreted in the feces; plasma clearance of barium into the feces may be threefold greater than plasma clearance into the urine (Liniecki, 1971). The range of reported oral absorption factors for all animal studies was 0.7%-85.0%. This large variation may be explained in part by differences in study duration (length of time gastrointestinal absorption was monitored), species, age, and fasting status of the animals; however, these experimental parameters did not affect gastrointestinal absorption of barium consistently among the different studies. The presence of food in the gastrointestinal tract appears to decrease barium absorption, and barium absorption appears to be higher in young animals as compared with older animals.

Richmond et al. (1960, 1962a,b) studied the gastrointestinal absorption of barium chloride in several animal species. Gastrointestinal absorption was approximately 50% in beagle dogs compared with 30% in rats and mice. Taylor et al. (1962) reported gastrointestinal absorption (that left in the carcass, after removal of the gastrointestinal tract, plus that recovered in urine) of 7%-8%, 20%, and 63%-84% of a single gavage dose of radiolabeled barium chloride in older (6-70 weeks) nonfasted, older fasted, and younger (14-22 days) nonfasted rats, respectively; absorption was measured only 7 h after administration of the barium, suggesting that the study may have been terminated prior to completion of absorption. Using the 30-day retention data from a study by Della Rosa et al. (1967), Cuddihy and Griffith (1972) estimated gastrointestinal absorption efficiencies of 0.7%-1.5% in adult beagle dogs and $\leq$ 7% in younger beagle dogs (43-250 days of age).

McCauley and Washington (1983) and Stoewsand et al. (1988) have compared absorption efficiencies of several barium compounds. Barium sulfate and barium chloride were absorbed at "nearly equivalent rates" (based on blood and tissue levels) in rats following a single gavage dose

of similar barium concentrations (McCauley and Washington, 1983). Similar concentrations of barium were found in the bones of rats fed diets with equivalent doses of barium chloride or barium from Brazil nuts. McCauley and Washington (1983) suggested that the similarity in absorption efficiency between barium sulfate and barium chloride may have been due to the ability of hydrochloric acid in the stomach to solubilize small quantities of barium sulfate. This is supported by the finding that barium carbonate in a vehicle containing sodium bicarbonate was poorly absorbed. The buffering capacity of sodium bicarbonate may have impaired the hydrochloric acid-mediated conversion to barium chloride. The results of these studies suggest that soluble barium compounds and/or barium compounds that yield a dissociated barium ion in the acid environment of the upper gastrointestinal tract have similar absorption efficiencies.

Barium sulfate is often considered to be a very poorly absorbed barium compound. The results of the McCauley and Washington (1983) study provide evidence that at low concentrations the absorption of barium sulfate is similar to barium chloride. High concentrations of barium sulfate are likely to exceed the ability of the gastric hydrochloric acid to convert barium sulfate to barium chloride. However, some of the barium sulfate will still be absorbed. Statistically significant increases in the levels of barium in the blood and urine were found in humans ingesting 58 to 400 g barium sulfate in radio-opaque contrast materials (Mauras et al., 1983; Claval et al., 1987).

3.1.2. Respiratory Tract Absorption

No data are available on respiratory tract absorption of barium in humans. Animal studies provide evidence that barium compounds, including poorly water-soluble compounds such as barium sulfate, are absorbed from the respiratory tract. Morrow et al. (1964) estimated that the biological half-time of $^{131}BaSO_4$ in the lower respiratory tract was 8 days in dogs inhaling 1.1 µg/L barium sulfate (count median diameter [CMD] of 0.10 µm, σ_g of 1.68) for 30-90 min. Twenty-four hours after an intratracheal injection of $^{133}BaSO_4$, 15.3% of the radioactivity was cleared from the lungs. The barium sulfate was cleared via mucociliary clearance mechanisms (7.9% of initial radioactive burden) and via lung-to-blood transfer (7.4% of radioactivity) (Spritzer and Watson, 1964). Clearance half-times of 66 and 88 days were calculated for the cranial and caudal regions of the trachea in rats intratracheally administered 2 µg $^{133}BaSO_4$ (CMD of 0.34 µm, σ_g of 1.7) (Takahashi and Patrick, 1987).

Differences in water solubility appear to account for observed differences in respiratory tract clearance rates for barium compounds. The clearance half-times of several barium compounds were proportional to solubility in dogs exposed to aerosols of barium chloride (activity median aerodynamic diameter [AMAD] of 2.3 µm, σ_g of 1.5), barium sulfate (AMAD of 1.0 µm, σ_g of 1.6), heat-treated barium sulfate (AMAD of 0.9 µm, σ_g of 1.4), or barium incorporated in fused montmorillonite clay particles (AMAD of 2.2 µm, σ_g of 1.7) (Cuddihy et al., 1974).

3.1.3. Dermal Absorption

No data are available on dermal absorption of barium compounds.

3.2. DISTRIBUTION

The highest concentrations of barium in the body are found in the bone; approximately 91% of the total body burden is in the bone (WHO, 1990). Reeves (1986) notes that osseous uptake of barium is 1.5 to 5 times higher than that of calcium or strontium. In the bone, barium is primarily deposited in areas of active bone growth (WHO, 1990). The uptake of barium into the bone appears to be rapid. One day after rats were exposed to barium chloride aerosols, 78% of the total barium body burden was found in the skeleton; by 11 days postexposure, more than 95% of the total body burden was found in the skeleton (Cuddihy et al., 1974).

The remainder of the barium in the body is found in soft tissues, i.e., aorta, brain, heart, kidney, spleen, pancreas, and lung (WHO, 1990). High concentrations of barium are sometimes found in the eye, primarily in the pigmented structures (Reeves, 1986). McCauley and Washington (1983) found that 24 h after administration of an oral dose of $^{131}BaCl_2$ to dogs, ^{131}Ba levels in the heart were three times higher than the concentration in the eye, skeletal muscle, and kidneys (concentrations in the eye, muscle, and kidneys were similar). Additionally, the levels in the heart, eye, skeletal muscle, and kidneys were higher than the whole-blood concentration, suggesting the ability of soft tissue to concentrate barium.

3.3. ELIMINATION AND EXCRETION

Barium is excreted in the urine and feces following oral, inhalation, and parenteral exposure. The feces is the primary route of excretion. At a normal intake level of 1.33 mg/day (1.24, 0.086, and 0.001 mg/day from food, water, and air, respectively), approximately 90% of the barium is excreted in the feces and 2% in the urine (Schroeder et al., 1972). Tipton et al. (1969) found similar results; in the two men studied, 95%-98% and 2%-5% of the daily barium intake was excreted in the feces and urine, respectively.

The biological half-time of barium is relatively short. Half-times of 3.6, 34.2, and 1,033 days were estimated using a three-component exponential function (Rundo, 1967). Following inhalation exposure to $^{140}BaCl_2$-$^{140}LaCl_2$ (AMAD of 1.6-2.1 µm, σ_g of 2.0), a physical half-time of 12.8 days was estimated in beagle dogs (Cuddihy and Griffith, 1972).

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY, CASE REPORTS, AND CLINICAL CONTROLS

4.1.1. Oral Exposure

Wones et al. (1990) administered barium (as barium chloride) in the drinking water of 11 healthy male volunteers (4 black and 7 white) whose ages ranged from 27 to 61 years (mean 39.5 and median 41 years of age). None of the subjects was taking any medications and none had hypertension, diabetes, or cardiovascular disease. Barium concentrations in the drinking water consumed by the subjects prior to the study were known to be very low. The subjects were given 1.5 L/day of distilled water containing various levels of barium chloride. No barium was added for the first 2 weeks, which served as a control period; 5 ppm barium (0.11 mg Ba/kg-day using 70 kg reference weight) was added for the next 4 weeks, and 10 ppm barium (0.21 mg Ba/kg-day) was added for the last 4 weeks of the study. Diets were controlled to mimic American dietary practices (barium content of the diet was not determined, but the authors mentioned that a typical hospital diet provides 0.75 mg Ba/day, or 0.011 mg Ba/kg-day using 70 kg reference weight). All beverages and food were provided, and subjects were instructed to consume only what was provided. The subjects were instructed to keep their level of exercise constant and to abstain from alcohol, and smokers were told to smoke consistently throughout the study. Systolic and diastolic blood pressures were measured in the morning and evening. Blood was collected at the beginning and periodically, particularly as four consecutive daily samples at the end of each of the three study periods. Twenty-four-hour urine collections were performed at the end of each study period. Twenty-four-hour continuous electrocardiographic monitoring was performed on 2 consecutive days at the end of each study period.

Blood pressures were not significantly affected by barium exposure at any dose level. No significant alterations in serum calcium levels were observed (9.11, 9.23, and 9.23 mg/dL at the 0, 5, and 10 ppm exposure levels, respectively). When the serum calcium levels were "normalized" for differences in albumin levels, a significant increase ($p = 0.01$) was observed (8.86, 9.03, and 9.01, respectively). This type of adjustment has been considered unreliable (Sutton and Dirks, 1986). The study authors attributed the increase in adjusted serum calcium levels to a slight decrease in serum albumin. The increase in serum calcium levels was considered borderline and not clinically significant. No significant changes were observed in plasma total cholesterol, triglyceride, LDL or HDL cholesterol, LDL:HDL ratio, and apolipoproteins A1, A2, and B; in serum glucose, albumin, and potassium levels; or in urinary levels of sodium, potassium, vanillymandelic [*sic*] acid, or metanephrines. Electrocardiograms revealed no changes in cardiac cycle intervals, including the QT interval; the study authors noted that the lack of shortening of the QT interval provided evidence that the slight increase in serum calcium was not clinically significant. In addition, no significant arrhythmias, no increase in ventricular irritability, and no apparent conduction problems were seen with barium exposure. A no-observable-adverse-effect level (NOAEL) of 0.21 mg Ba/kg-day can be determined from the 10 ppm barium exposure regime that was used for the last 4 weeks of the study.

Brenniman and Levy (1984) reported a retrospective epidemiology study of mortality and morbidity in populations living in communities in Illinois with elevated levels of barium in municipal drinking water (≥ 2-10 mg/L, 0.06-0.3 mg Ba/kg-day assuming water consumption of 2 L/day and weight of 70 kg) or low levels of barium in drinking water (≤ 0.2 mg/L, 0.006 mg Ba/kg-day). Portions of this study were published previously (Brenniman et al., 1979, 1981). Barium was the only drinking water contaminant that exceeded drinking water regulations of the time in any of the public drinking water supplies. The communities were matched for demographic characteristics and socioeconomic status. Communities that were industrialized or geographically different were excluded. Although the study attempted to exclude communities with high rates of population change, two of the four high-barium communities had about 75% change in population between 1960 and 1970, but were kept in the study for lack of satisfactory replacements.

In the mortality study, age-adjusted mortality rates for cardiovascular diseases (combined), heart diseases (arteriosclerosis), and all causes for both sexes together were significantly ($p \leq 0.05$) higher in the elevated barium communities compared with the low-barium communities for the years 1971-1975. These differences were largely confined to the population 65 years old or older. This study did not control for several important variables such as population mobility (approximately 75% turnover in two of the four high-barium communities from 1960 to 1970), use of water softeners that would remove barium from and add sodium to the water supply, use of medication by study subjects, and other risk factors such as smoking, diet, and exercise. As a result, it is not possible to assign a causal relationship between mortality and exposure to barium.

The morbidity study was conducted on two communities, McHenry and West Dundee, IL, which had similar demographic and socioeconomic characteristics, but a 70-fold difference in barium concentrations in drinking water. The mean concentration in McHenry's drinking water was 0.1 mg Ba/L, whereas the mean concentration in West Dundee's drinking water was 7.3 mg Ba/L. The levels of other minerals in the drinking water of the two communities were stated to be similar. Subjects were selected randomly from a pool that included every person 18 years of age or older in a random sample of blocks within each community. All subjects underwent three blood pressure measurements (taken over a 20-min period with a calibrated electronic blood pressure apparatus) and responded to a health questionnaire that included such variables as sex, age, weight, height, smoking habits, family history, occupation, medication, and physician-diagnosed heart disease, stroke, and renal disease. Data were analyzed using the signed ranked test for age-specific rates, the weighted Z test for prevalence rates, and analysis of variance for blood pressures. No significant differences in mean systolic or diastolic blood pressures or in rates of hypertension, heart disease, stroke, or kidney disease were found for men or women of the two communities. A more controlled study was conducted on a subpopulation of the McHenry and West Dundee subjects who did not have home water softeners, were not taking medication for hypertension, and had lived in the study community for more than 10 years. No significant differences were observed between the mean systolic or diastolic blood pressures for men or women of these subpopulations in the low-barium (0.1 mg Ba/L, 0.0029 mg Ba/kg-day

assuming water ingestion of 2 L/day and 70 kg weight) and elevated-barium communities (7.3 mg Ba/L, 0.21 mg Ba/kg-day). Thus, the dosage associated with the elevated barium levels, 0.21 mg Ba/kg-day, is a NOAEL for hypertension and possibly for kidney disease as well, although kidney disease was addressed only by the health questionnaire.

A study of trace elements in ribs of elderly Japanese people and the presence of three chronic diseases—cancer, cerebrovascular damage (infarction or hemorrhage in the cerebrum), and osteoporosis or transcervical and vertebral fracture—at autopsy reported that mean rib barium concentrations were higher in the cases that were positive for cerebrovascular damage than in those that were negative (Yoshinaga et al., 1995). The people had no known occupational exposure to trace elements. Potential risk factors (other than trace element levels in bone) for these conditions were not investigated. In addition, the association between bone barium levels and cerebrovascular damage applied only when the bone analyses were performed by inductively coupled plasma mass spectrometry (and not by other techniques). The number of cases analyzed by this technique was only 35. Thus, although the results are consistent with a potential cerebrovascular effect of barium, the value of this study in assessing the toxicity of barium is questionable.

4.1.2. Inhalation Exposure

The database on the toxicity of inhaled barium compounds in humans consists primarily of studies of occupational exposure to barium sulfate or barite ore or to unspecified soluble barium compounds. Several case reports (e.g., Pendergrass and Greening, 1953; Seaton et al., 1986) and a prospective study conducted by Doig (1976) have reported baritosis in barium-exposed workers. Baritosis is considered a benign pneumoconiosis resulting from the inhalation of barite ore or barium sulfate. The most outstanding feature of baritosis is the intense radiopacity of the discrete opacities that are usually profusely disseminated throughout the lung fields; in some cases the opacities may be so numerous that they appear confluent. The Third Conference of Experts on Pneumoconiosis (ACGIH, 1992) noted that barium sulfate produced a noncollagenous type of pneumoconiosis in which there is a minimal stromal reaction that consists mainly of reticulin fibers, intact alveolar architecture, and potentially reversible lesions. The available human data on baritosis suggest that the accumulation of barium in the lungs does not result in medical disability or symptomatology. A decline in the profusion and opacity density, suggesting a decrease in the amount of accumulated barium in the lung, has been observed several years after termination of exposure. Studies by the National Institute for Occupational Safety and Health (NIOSH, 1982) and Zschiesche et al. (1992) on soluble barium compounds did not include radiography; these studies focused on the potential for barium to induce systemic effects (e.g., increases in blood pressure, kidney effects, electrocardiogram [EKG] alterations).

Doig (1976) conducted a prospective study on workers at a barite grinding facility. During the initial investigation in 1947, five workers employed for more than 3.5 years were

examined. No evidence of baritosis was observed in any of the workers. In 1961, eight workers (26-45 years of age, mean of 32 years) employed for 3.5-18 years (mean of 9 years) were examined (one of these workers was also examined in 1947). Seven of the workers reported no respiratory symptoms; one worker reported a slight occasional cough. No abnormal symptoms were noted during the physical examination of seven of the workers; crepitations dispelled by cough were observed in one worker (not the same worker reporting an occasional cough). Pneumoconiosis was detected in the radiographs of seven workers. Three other workers employed for 1 mo to 1 year were also examined in 1961. Two of these workers reported having slight coughs, but no abnormal findings were observed during the physical examination and the chest radiographs were normal. At this time, dust concentrations ranging from 2,734 to 11,365 particles per cubic mL were measured using a thermal precipitator; the concentration of barium in the dust was not measured. Barite samples were analyzed for quartz, silica, and iron content. No quartz was detected, and the total silica and total iron (as Fe_2O_3) concentrations were 0.07%-1.96% and 0.03%-0.89%, respectively.

Ten of the eleven workers examined in 1961 were reexamined in 1963 (18 mo later). Two new cases of pneumoconiosis were diagnosed. Thus, 9 of 10 workers exposed to barium sulfate for 1.5 to 19.5 years (mean of 8.2 years) had well-marked baritosis. Three of these workers reported a slight or occasional cough and none had dyspnea. Among the nine workers with baritosis, three did not smoke, four smoked $\leq$ 1 pack/day, and two smoked > 1 pack/day. In six of the seven workers with previously diagnosed baritosis, no significant changes in the degree of pneumoconiosis were observed; an increase in the number of opacities was observed in the seventh worker. Spirometric lung function tests (vital capacity, flow rate, and forced expiratory volume) were performed in five workers. For three of these workers, the results of the lung function tests were similar to predicted normal values (89%-119% of predicted values). Lung function was below normal in the other two workers (70%-85% of predicted values). It is questionable whether the impaired lung function was related to barium exposure. One of the two workers was an alcoholic and heavy smoker, and the other had a fibrotic right middle lung lobe that probably resulted from a childhood illness.

In 1964, the barite grinding facility closed. Follow-up examinations were performed in 1966, 1969, and 1973 on five of the workers. Termination from barium exposure resulted in a decline in the profusion and density of opacities. In 1966, there was slight clearing of opacities; by 1973, there was a marked decrease in profusion and density. No significant changes in lung function were observed during this 10-year period.

NIOSH (1982) conducted a health survey of past and present workers at the Sherwin Williams Company's Coffeyville, KS, facility. Work performed at the facility included grinding, blending, and mixing mineral ores. At the time of the study, four processes were in operation: "ozide process," which involved blending several grades of zinc oxide; "ozark process," which involved bagging very pure zinc oxide powder; "bayrite process," which involved grinding and mixing several grades of barium-containing ores; and "sher-tone process," which involved mixing inert clays with animal tallow. A medical evaluation was performed on 61 current

workers (91% participation) and 35 laid-off or retired workers (27% participation). Information on demographics, frequency of various symptoms occurring during the past 2 mo, chemical exposure, occupational history, smoking history, and history of renal disease, allergies, and hypertension was obtained from directed questionnaires. In addition, spot urine and blood samples and blood pressure measurements were taken. Exposures to barium, lead, cadmium, and zinc were estimated from 27 personal samples collected over a 2-day period. In the seven personal breathing zone samples collected from the bayrite area, the levels of soluble barium ranged from 87.3 to 1,920.0 µg/m^3 (mean of 1,068.5 µg/m^3), lead levels ranged from not detected to 15.0 µg/m^3 (mean of 12.2 µg/m^3, excluding the two no-detect samples), zinc levels ranged from 22.4 to 132.0 µg/m^3 (mean of 72 µg/m^3), and all seven samples had no detectable levels of cadmium. Soluble barium was also detected in breathing zone samples in the ozark area (10.6-1,397.0 µg/m^3, mean of 196.1 µg/m^3), ozide area (11.6-99.5 µg/m^3, mean of 46.8 µg/m^3), and sher-tone area (114.3-167.5 µg/m^3, mean of 70.45 µg/m^3).

Two approaches were used to analyze the results of the health survey. In the first approach, the workers were divided into five groups based on current job assignments. Of the 61 current workers, 14 worked in the bayrite area. No statistically significant increases in the incidence of subjective symptoms (e.g., headache, cough, nausea) or differences in mean blood lead levels, number of workers with blood lead levels of greater than 39 µg/dL, mean free erythrocyte protoporphyrin (FEP) levels, mean hematocrit levels, mean serum creatinine levels, number of workers with serum creatinine levels of greater than 1.5 mg/dL, number of workers with blood urea nitrogen (BUN) levels of greater than 20 mg/dL, blood pressure, or mean urine cadmium levels were observed between the different groups of workers. In the second approach, the workers were divided into seven groups based on past job assignments. One group consisted of 12 workers working in barium process areas (bayrite process and other processes no longer in operation at the facility that involved exposure to barium ores and barium carbonate) for at least 5 years; barium exposure levels were not reported for this group of workers. The results of the health survey for the barium-exposed workers were compared with results for 25 workers who stated that they had never worked in barium process areas. No statistically significant differences in mean age, number of years employed, number of current or past smokers, prevalence of subjective symptoms, mean FEP levels, mean hematocrit levels, mean urine cadmium levels, mean β2-microglobulin levels, or the prevalence of workers with elevated serum creatinine, BUN, or urine protein levels were observed between the two groups. The number of workers with elevated blood pressure (defined as systolic pressure ≥ 140 mm Hg or diastolic pressure ≥ 90 mm Hg, or taking medication for hypertension) was significantly higher ($p = 0.029$) in the barium-exposed group (7/12, 58%) than in the comparison group (5/25, 20%). The number of workers in the barium group with blood lead levels of > 39 µg/dL was lower than in the comparison group (0% vs. 28%); however, the difference was not statistically significant ($p = 0.072$). Additionally there was no significant difference between mean blood lead levels in the barium-exposed workers (24 µg/dL) and the comparison group (32 µg/dL). Although the results of this study suggest an association between exposure to barium and hypertension, the results should be interpreted cautiously because (1) a small number of workers were examined, (2) it appears that blood pressure was measured only once, and (3) the workers were exposed to a

number of other chemicals, including lead, which is associated with an increase in blood pressure.

The health effects associated with occupational exposure to barium during arc welding with barium-containing stick electrodes and flux-cored wires were investigated by Zschiesche et al. (1992). A group of 18 healthy welders not using barium-containing consumables in the past 10 days were divided into three groups: group A (n = 8, mean age of 30.4 years) performed arc welding with barium-containing stick electrodes, group B (n = 5, mean age of 43.6 years) performed arc welding with barium-containing self-shielded flux-cored wires, and group C (n = 5, mean age of 32.0 years) performed arc welding with barium-containing self-shielded flux-cored wires using welding guns with built-in ventilation systems. All welders performed welding with barium-free consumables on Thursday and Friday of the first week of the study. Barium-containing consumables were used during week 2 of the study and on Monday of week 3. The subjects welded for an average of 4 h per day. The average barium concentrations in the breathing zones were 4.4 (range of 0.1-22.7), 2.0 (0.3-6.0), and 0.3 (0.1-1.5) mg/m^3 for groups A, B, and C, respectively. No exposure-related subjective symptoms of health or neurological signs were found. No significant differences between pre- and postshift EKG, pulse rate, whole blood pH, base excess and standard bicarbonate, and plasma concentrations of sodium, magnesium, and total and ionized calcium were observed. During week 2, decreases in plasma potassium concentrations were observed in groups A and C; the levels returned to the normal range under continuation of barium exposure and were not statistically different from levels during week 1 (no barium exposure). This drop in serum potassium levels was not observed in group B, which had a similar barium exposure level as group A.

4.2. PRECHRONIC/CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

4.2.1. Oral Exposure

4.2.1.1. *Animal Studies With Adequate Diets*

Toxicity and carcinogenicity studies of barium chloride dihydrate were conducted by administering the chemical to rats and mice in drinking water for 13 weeks and for 2 years (NTP, 1994). A preliminary report of the subchronic studies was published earlier by Dietz et al. (1992).

In the subchronic studies (NTP, 1994), male and female B6C3F1 mice (10 animals/dose group/sex) received barium chloride dihydrate in drinking water at concentrations of 0, 125, 500, 1,000, 2,000, and 4,000 ppm for 13 weeks (95 days). Using the weekly water consumption and body weight data, the authors estimated the daily doses for the treated groups as 15, 55, 100, 205, and 450 mg Ba/kg-day for the males and 15, 60, 110, 200, and 495 mg Ba/kg-day for the females. The animals were fed NIH-07 pellets; the barium content of the diet was not reported.

Complete histopathological examinations were performed on all mice in the control, 2,000 ppm, and 4,000 ppm groups, and histopathological examinations of the kidneys were performed on the male mice in the 1,000 ppm group. Organ and body weights were measured, and neurobehavioral assessments (at 0, 45, and 90 days) were performed on animals of all groups. Cardiovascular studies and hematologic and serum electrolyte analyses were not performed on the mice.

At 4,000 ppm, 6/10 male and 7/10 female mice died; survivors appeared debilitated. At 125 ppm, 1/10 male mice died. All but one death occurred on or after week 5; the authors did not discuss cause of death. No animals died at other dosage levels. Water consumption in the male mice receiving 4,000 ppm was 18% lower than that of controls; in other groups water consumption was similar to that of controls. At 4,000 ppm, body weights of both sexes were significantly reduced, with final body weights 30%-50% lower than those for controls; absolute kidney weights were decreased in the males, and relative kidney weights were increased in the females; and absolute and relative thymus weights were decreased in both sexes. Decreased relative and/or absolute liver weights were seen in females at $\geq$ 1,000 ppm and in males only at the high dose.

Chemical-related nephropathy (kidney injury) occurred in 10/10 male and 9/10 female mice of the 4,000 ppm group. Lesions were characterized by tubule dilatation, renal tubule atrophy, tubule cell regeneration, and the presence of crystals primarily in the lumen of the renal tubules. Lymphoid depletions in the spleen, thymus, and lymph nodes were observed in the high-dose mice that died during the study, and these depletions were attributed to the reduced body weight and stress. No other histopathological changes were observed in any tissues, including the liver.

A statistically significant decrease in forelimb grip strength was observed at day 90 in female mice receiving 4,000 ppm. According to the authors, this finding may have been due to debilitation of the animals. No significant dose-related changes were observed in the other neurobehavioral endpoints (undifferentiated motor activity, thermal sensitivity judged by a tail flick latency test, startle-response to acoustic and air-puff stimuli, or hindlimb grip strength or hindlimb foot splay).

Thus, for the mice, 4,000 ppm of barium in the drinking water (450 and 495 mg Ba/kg-day for the males and females) constitutes a subchronic FEL for nephropathy and mortality. The next lower dose, 2,000 ppm (205 and 200 mg Ba/kg-day) constitutes a subchronic NOAEL. Although absolute and relative liver weights were significantly decreased in the female mice at this dose level, no histopathological effects on the liver were seen at any dose level, so the effect is judged nonadverse.

In the same subchronic study (NTP, 1994), male and female F344/N rats (10 animals/dose group/sex) received drinking water containing 0, 125, 500, 1,000, 2,000, and 4,000 ppm barium chloride dihydrate for 13 weeks (95 days). Using the weekly water consumption and body weight data, the authors estimated doses for the treated groups as 10, 30, 65, 110, and 200 mg Ba/kg-day for males and 10, 35, 65, 115, and 180 mg Ba/kg-day for females. The animals were fed NIH-07 pellets; the barium content of the diet was not reported. Complete

histopathological examinations were performed on all rats in the control and 4,000 ppm groups. In addition, histopathological examinations were performed on the kidney, liver, spleen, and thymus of all rats in the 2,000 ppm group and on the adrenal gland, heart, and salivary gland of female rats in the 2,000 ppm group. Hematological and serum electrolyte values, organ and body weights, neurobehavioral assessments (at 0, 45, and 90 days), and cardiovascular studies (heart rate, systolic blood pressure, and analysis of electrocardiograms) were recorded.

At 4,000 ppm, 3/10 male and 1/10 female rats died during the last week of the study. These deaths were considered by the authors to be chemical related; cause of death was not evident on histopathological examination. No animals died at lower dosage levels. Water consumption in the male and female rats receiving 4,000 ppm was decreased by 30% relative to that of controls. Body weights of males and females, at this dosage, were significantly reduced by approximately 13% and 8%, respectively, in comparison with the controls. The barium-related organ weight changes consisted of decreased absolute and/or relative liver weights in both sexes at 4,000 ppm, increased absolute and relative kidney weights in female rats at $\geq$ 2,000 ppm, and increased relative kidney weights in male rats at 4,000 ppm. Depression of the absolute thymus weights occurred at 4,000 ppm in female rats. The authors attributed the differences in relative or absolute organ weights at 4,000 ppm in organs other than the kidney to the decrease in mean body weights. Organ weight changes in the kidney were considered to be associated with chemical-induced renal lesions.

Chemical-related kidney lesions occurred in 3/10 male and 3/10 female rats at 4,000 ppm. The lesions were limited to minimal to mild, focal to multifocal areas of dilatation of the proximal convoluted tubules. Crystals were not present in the kidney tubules. No such renal lesions were seen in controls or the lower dose groups. The chemical-related kidney lesions were different from the spontaneous early lesions of nephropathy that occur in rats. Lymphoid depletions in the spleen and thymus were observed in the rats receiving 4,000 ppm that died during the study. No other histological changes were observed.

Statistically significant decreases in the magnitude of undifferentiated motor activity were observed at day 90 in rats of both sexes at 4,000 ppm. Marginal decreases were seen in all other barium-exposed groups except the 1,000 ppm females. No significant or dose-related changes were observed in the other neurobehavioral endpoints (thermal sensitivity judged by a tail flick latency test, startle-response to acoustic and air-puff stimuli, forelimb or hindlimb grip strength, or hindlimb foot splay). The preliminary report of this study (Dietz et al., 1992) stated that there were no consistent effects on behavior produced by barium chloride dihydrate and that the neurobehavioral changes were attributable to the general condition of the high-dose rats and mice. The final report by NTP (1994), however, did not discuss the toxicological significance of the neurobehavioral test results in rats.

Serum electrolyte determinations indicated that serum phosphorus was significantly elevated in female rats at $\geq$ 500 ppm and in male rats at $\geq$ 2,000 ppm, but serum phosphorus did not increase with increasing dose in the affected groups. Dietz et al. (1992) and NTP (1994) stated that these elevations may have reflected renal tubule damage. Dietz et al. (1992) considered the biological significance of this change in females to be marginal because of control values that were lower than historical control values. The NTP (1994) concluded that the

elevated values probably were due to an artifact from hemolysis of the collected blood samples, because the renal tubule lesions in rats were minimal to mild in severity. No other chemical-related or biologically significant changes in serum electrolytes or in hematology values were seen. Cardiovascular studies in the rats revealed no barium-associated differences in heart rate, systolic blood pressure, or electrocardiogram.

Thus, in the rats, 4,000 ppm barium in the drinking water (200 mg Ba/kg-day for males and 180 mg Ba/kg-day for females) constitutes a subchronic FEL for mortality. Renal histopathological lesions were seen at this dose level but were not severe. Detection of glomerular effects, however, would have required electron microscopy or urinalysis, neither of which was performed. Glomerular effects were seen during electron microscopic examination in unilaterally nephrectomized rats given 1,000 ppm barium (150 mg Ba/kg-day) through the drinking water in a study by McCauley et al. (1985). The next lower dose level in the NTP (1994) study, 2,000 ppm (110 mg Ba/kg-day for males and 115 mg Ba/kg-day for females), may be a subchronic lowest-observable-adverse-effect level (LOAEL) for renal effects in females based on the increased absolute and relative kidney weight changes. The subchronic NOAEL would be 1,000 ppm (65 mg Ba/kg-day for both sexes).

In the chronic study (NTP, 1994), male and female B6C3F1 mice (60 animals/dose group/sex) received barium chloride dihydrate in drinking water at concentrations of 0, 500, 1,250, or 2,500 ppm for 103 weeks (males) and 104 weeks (females). The authors estimated the daily doses for the treated groups using measured water consumption and body weights as 30, 75, and 160 mg Ba/kg-day for males, and 40, 90, and 200 mg Ba/kg-day for females. The animals were fed an NIH-07 mash diet; the barium content of the diet was not reported. At the 15-mo interim evaluation, venous blood was collected from all mice for hematology and clinical chemistry. In addition, a limited number of mice (9, 10, 10, and 10 males and 10, 7, 10, and 6 females from the 0, 500, 1,250, and 2,500 ppm groups, respectively) were sacrificed at 15 mo. The remaining animals continued on the study until they were moribund, died naturally, or were sacrificed at the end of the study. Necropsy and complete histopathological examinations were performed on all animals. Body weights were monitored and organ weights were determined at 15 mo. Neurobehavioral and cardiovascular studies were not performed.

At the 15-mo interim evaluation, the absolute and relative spleen weights of the female mice that received 2,500 ppm were significantly lower than those of the controls, and the absolute and relative thymus weights of high-dose male mice that received 2,500 ppm were marginally lower than those of the controls. Determination of hematology and clinical chemistry parameters (e.g., phosphorus, calcium, and urea nitrogen) at the 15-mo interim evaluation showed no significant differences between control and exposed mice.

At 2,500 ppm, survival rates for mice at the end of study (65% for males and 26% for females) were significantly lower than those of the controls (89% for males and 76% for females). The reduction in survival became apparent in females at week 15 and in males at week 65 and was attributed to chemical-related renal lesions. Survival was not significantly lower relative to controls at the lower dosage levels. In male and female high-dose mice, the final mean body weights were 8% and 12% lower, respectively, than those of the corresponding control groups. Water consumption was not affected by barium.

The incidence of nephropathy at the end of the study was significantly increased in mice receiving 2,500 ppm. In order of controls through highest dose, incidences were 1/50, 0/50, 2/48, and 19/50 in males and 0/50, 2/53, 1/50, and 37/50 in females. The nephropathy at the highest dose was chemical related and morphologically distinct from the spontaneous degenerative lesions commonly observed in aging B6C3F1 mice. The lesions were characterized by tubule dilatation, renal tubule atrophy, tubule cell regeneration, hyaline cast formation, multifocal interstitial fibrosis, and the presence of crystals, primarily in the lumen of the renal tubules. Lymphoid depletions in the spleen, thymus, and lymph nodes were observed in high-dose male and female mice, particularly in animals that died early, and were thought to be the result of debilitation associated with nephropathy. There were no other chemical-related histological changes.

Thus, in mice, 2,500 ppm barium in the drinking water (160 mg Ba/kg-day for males and 200 mg Ba/kg-day for females) constitutes a chronic FEL for severe nephropathy and decreased survival in the NTP (1994) study. The next lower exposure level, 1,250 ppm (75 mg Ba/kg-day in males and 90 mg Ba/kg-day in females), is a chronic NOAEL.

The incidences of neoplasms in the barium-exposed mice were not significantly higher than in control mice. In the 2,500 ppm female mice, the incidences of several neoplasms were significantly lower than in the controls; the authors attributed this finding to the marked reduction in survival in the barium-exposed animals.

In the same chronic study (NTP, 1994), male and female F344/N rats (60 animals/dose group/sex) received drinking water containing 0, 500, 1,250, or 2,500 ppm barium chloride dihydrate for 104 weeks (males) or 105 weeks (females). The authors estimated daily doses for the treated groups using measured water consumption and body weights as 15, 30, and 60 mg Ba/kg-day for males, and 15, 45, and 75 mg Ba/kg-day for females. The animals were fed an NIH-07 mash diet; the barium content of the diet was not reported. For a 15-mo interim evaluation, venous blood was collected from all rats for hematology and clinical chemistry. In addition, a limited number of rats (10 from each group) were sacrificed at 15 mo. The remaining animals stayed on the study until they were moribund, died naturally, or were terminally sacrificed. Necropsy and complete histopathological examinations were performed on all animals. Body weights were monitored throughout the study, and organ weights were determined in the animals killed at 15 mo. Neurobehavioral and cardiovascular studies were not performed.

A marginally increased survival of exposed male groups (percent probability of survival: 62%, 58%, and 67% for the 500, 1,250, and 2,500 ppm groups, respectively) compared with that of the male controls (44%) was attributed to a decreased incidence of leukemia. Survival of the females was not significantly affected. For male rats receiving 2,500 ppm, the final mean body weights were 5% lower than for controls. The final mean body weights of females receiving 1,250 and 2,500 ppm were 6% and 11% lower, respectively, than those of controls. Water consumption was decreased in a dose-related manner; at the highest exposure level the decrease, relative to controls, was 22% in males and 25% in females.

Absolute and relative organ weights, determined only at the 15-mo interim evaluation, were not affected in the males. In the females, a statistically significant ($p \leq 0.01$) increase in relative kidney weights occurred at 2,500 ppm. Body weights in the females at 15 mo were decreased by 9% at 2,500 ppm in comparison with controls, whereas kidney weights in this group were slightly increased relative to those of controls. Determination of hematology values and clinical chemistry values (e.g., phosphorus, calcium, and urea nitrogen) at the 15-mo interim evaluation showed no significant differences between control and exposed rats.

Chemical-related kidney lesions were not observed in rats in these 2-year studies; the only potential indication of renal toxicity was the increased relative kidney weight seen in the females at 2,500 ppm. In addition, there were no chemical-related histological changes in any other organs or tissues. Thus, the highest exposure level tested in this study, 2,500 ppm barium in drinking water (60 mg Ba/kg-day for males and 75 mg Ba/kg-day for females), may be a chronic NOAEL or LOAEL for rats, depending on interpretation of the increased relative kidney weight in females. When considered together with the results in the 13-week NTP (1994) study in rats, in which increased relative and absolute kidney weights were seen in female rats receiving 2,000 ppm barium in drinking water (115 mg Ba/kg-day) and kidney lesions and greater increases in relative and absolute kidney weights were seen in female rats at 4,000 ppm (180 mg Ba/kg-day), the increased relative kidney weight in females of the 2-year study are suggestive of potential renal effects. Therefore, 75 mg Ba/kg-day is designated a chronic LOAEL and 45 mg Ba/kg-day a chronic NOAEL for female rats for renal effects in the NTP (1994) study.

No statistically significant increases in the incidence of neoplasms were observed in the barium-exposed rats. Significant negative trends were observed in the incidence of mononuclear cell leukemia in male rats (35/50, 25/50, 26/50, and 15/50 in 0, 500, 1,250, and 2,500 ppm groups, respectively), benign and malignant adrenal medulla pheochromocytoma in male rats (13/49, 11/50, 12/49, and 6/50, respectively), and mammary gland neoplasms (fibroadenoma, adenoma, or carcinoma) in female rats (17/50, 21/50, 13/50, and 11/50, respectively). Additionally, the incidences of mononuclear cell leukemia in the male rats exposed to 500, 1,250, and 2,500 ppm and adrenal medulla pheochromocytoma in male rats exposed to 2,500 ppm were significantly lower than the incidences in the controls.

McCauley et al. (1985) reported histological, electron microscopic, electrocardiograph, and blood pressure studies in rats given barium in their drinking water for various durations and fed Purina rat chow (contributing significant barium intake) or Tekland rat chow (insignificant barium intake). In the histology studies, CD Sprague-Dawley rats were fed Purina rat chow containing 12 ppm barium. The three exposure regimens were as follows: (1) male CD Sprague-Dawley rats (12/group) were exposed to 0, 1, 10, 100, or 250 ppm barium (barium chloride) in drinking water for 36 weeks; (2) female CD Sprague-Dawley rats (12/group) were exposed to 0 or 250 ppm barium in drinking water for 46 weeks; and (3) male CD Sprague-Dawley rats (10/group) were exposed to 0, 1, 10, or 100 ppm barium in drinking water for 68 weeks. The authors reported that no significant differences in food or water intake or body weight were observed, but they did not report the actual data. They stated that rats receiving 10 ppm barium in the drinking water ingested 1.5 mg Ba/kg-day from water and 1 mg Ba/kg-day from the Purina diet. This barium intake was used to estimate total barium intake for the other exposure levels.

Thus, the estimated total barium intakes were 1, 1.15, 2.5, 16, and 38.5 mg/kg-day for the 0, 1, 10, 100, and 250 ppm concentrations for all exposure regimens.

Histological evaluations of an extensive number of tissues, including gastrointestinal tract, liver, heart, adrenal gland, brain, respiratory tract, spleen, thymus, kidneys, ovaries, and testes, did not reveal barium-related lesions. No alterations in hematocrit levels were observed. A retinal lesion ("focal absence of the outer layers of the retina") was observed in 5/12 males exposed to 100 ppm but 0/11 males exposed to 250 ppm for 36 weeks, 7/12 females exposed to 250 ppm for 46 weeks, 1/10 male controls exposed for 68 weeks, and 2/10 males in each of the 1, 10, and 100 ppm groups exposed for 68 weeks. Because this lesion does not appear to be dose- or duration-related, its relationship to barium exposure is uncertain. Retinal dystrophy is common in CD Sprague-Dawley rats (Schardein et al., 1975); incidence depends on intensity of light and cage composition (clear plastic or stainless steel) and cage position in relation to light sources (Bellhorn, 1980). No significant increases in the incidence of neoplasms were observed in the barium-exposed rats, but the study duration is less than a lifetime and would have missed late-developing tumors.

In the electrocardiographic study, CD Sprague-Dawley rats (10-11/group, sex not specified) were given drinking water containing 0 or 250 ppm barium (as barium chloride) for 5 mo and Purina rat chow (estimated intakes of 1 and 38.5 mg Ba/kg-day, based on the estimates for the histology study). Data were obtained at 0, 4, and 60 min after an intravenous injection of 0.5 µg/kg of L-norepinephrine (NE). Barium induced a significant enhancement of NE-induced bradycardia compared with controls 4 min after NE administration, but by 60 min, the heart rates of controls were still depressed, whereas those of barium-exposed animals were approaching normal. No significant alterations in the PR, QS, QT, and ST interval durations or peak amplitudes were observed. The toxicological significance of these findings is uncertain.

In the blood pressure study, CD Sprague-Dawley rats (6/group, sex was not specified) were fed Tekland rat chow (0.5 µg Ba/kg-day) and administered barium in drinking water for 16 weeks. Normotensive rats received 0, 3, 10, 30, or 100 ppm barium in drinking water or in 0.9% sodium chloride solution as drinking water. Unilaterally nephrectomized rats received 1, 10, 100, or 1,000 ppm barium in regular drinking water or in 0.9% sodium chloride as drinking water. Using data from the histology study, the doses corresponding to 0, 1, 3, 10, 30, 100, and 1,000 ppm were estimated to be 0, 0.15, 0.45, 1.5, 4.5, 15, and 150 mg Ba/kg-day, respectively. All of these groups showed fluctuations of blood pressure but no hypertension. Dahl salt-sensitive rats, exposed to 1, 10, 100, or 1,000 ppm barium in 0.9% sodium chloride for 16 weeks, had a transiently elevated blood pressure (approximately 150-160 mm Hg) during the first 1-2 weeks of exposure to 1 or 10 ppm barium. The response at the 1 and 10 ppm barium levels was explained as a normal response to the 0.9% sodium chloride in the drinking water. Blood pressure during the remaining period of exposure to 1 or 10 ppm barium or during the entire period of exposure to 100 or 1,000 ppm barium was not indicative of hypertension. No hypertension was seen in Dahl salt-resistant rats given the same exposures. Thus, there was no indication that barium contributed to hypertension, but further interpretation of the results is problematic because of the lack of 0 ppm barium/0.9% sodium chloride control groups.

Electron microscopic examination of kidneys in all the rats in the blood pressure studies demonstrated no histopathologic changes in arteriolar vessel walls or in tubules of the nephrons. However, structural changes in glomeruli (fused podocyte processes and thickening of the capillary basement membrane, and myelin figures in Bowman's space) were observed in the 1,000 ppm groups. These changes are indicative of damage to the glomerulus that would be evidenced as inefficient glomerular filtration, including proteinuria. The only groups that received 1,000 ppm barium were the unilaterally nephrectomized rats that received barium in regular drinking water or in 0.9% sodium chloride solution, and Dahl salt-sensitive and salt-resistant rats that received barium in 0.9% sodium chloride. Normal CD Sprague-Dawley rats were not tested at this exposure level. No glomerular effects were seen at the next lower exposure level, 100 ppm, in any group of rats, including normal CD Sprague-Dawley rats that received barium in regular drinking water.

Thus, the study by McCauley et al. (1985) detected no adverse effect of barium on blood pressure at drinking water exposure levels up to 1,000 ppm (150 mg Ba/kg-day), the highest level tested. The only effect seen was glomerular damage in unilaterally nephrectomized rats that received 1,000 ppm barium in drinking water (150 mg Ba/kg-day). The NOAEL for glomerular effects in this study is 100 ppm (15 mg Ba/kg-day) in both unilaterally nephrectomized and intact rats. The McCauley et al. (1985) study is the only study that examined the kidney for glomerular effects and also measured blood pressure. The applicability of dose-response data from renal toxicity studies in unilaterally nephrectomized rats to intact rats or humans is uncertain, however, because removal of renal tissue may affect sensitivity of the remaining tissue to nephrotoxins. A reduction in renal mass, such as that produced by partial nephrectomy, results in compensatory adaptation of the remnant kidney tissue and associated changes in cellular metabolism and function that may affect the sensitivity of the animal to nephrotoxicity. These changes include cellular hypertrophy and increased transport activity in the proximal and distal tubule, changes in renal metabolism, and increased renal plasma flow and glomerular filtration rate (Zalups et al., 1987). Increased, decreased, or no change in susceptibility to nephrotoxicity has been demonstrated in rats that have undergone unilateral or three-quarter nephrectomy, depending on the chemical (Zalups and Lash, 1990; Zalups et al., 1988). At present, it is not possible to reliably predict which chemicals are likely to be more or less toxic or to have no change in toxicity to unilaterally nephrectomized rats.

Tardiff et al. (1980) exposed male and female Charles River rats (30 animals/dose group/sex) continuously to 0, 10, 50, or 250 ppm barium (as barium chloride) in drinking water for 4, 8, or 13 weeks. The authors estimated mg Ba/kg-day doses for the treated groups as 1.7, 8.1, and 38.1 for males and 2.1, 9.7, and 45.7 for females. Rats were fed a diet of Tekland mouse/rat diet pellets, which contributed a baseline dose of 0.5 µg Ba/kg-day. No deaths occurred, and there were no clinical signs of toxicity. Food consumption and body weights in the treated groups were essentially the same as in the control groups. Water consumption, however, was depressed in both sexes at 250 ppm barium. Slight decreases in relative adrenal weights occurred in males at $\geq$ 50 ppm at 8 weeks and in females at all barium concentrations at 13 weeks, but these changes were not dose related, and a slight increase occurred in females at 250 ppm at 8 weeks. No treatment-related changes were seen in hematologic parameters, serum alkaline phosphatase, SGOT, SGPT, BUN, serum ions (sodium, potassium, calcium), gross pathology, and histopathology of the liver, kidneys, spleen, heart, brain, muscle, femur, and

adrenal glands. Blood pressure and endpoints sensitive for glomerular damage (electron microscopic examination or urinary excretion of protein) were not investigated. This study identifies a subchronic NOAEL of 250 ppm (38.1-45.7 mg Ba/kg-day).

4.2.1.2. *Animal Studies With Restricted Diet*

Perry et al. (1983, 1985, 1989) exposed female weanling Long-Evans rats to 0, 1, 10, or 100 ppm barium (barium chloride) in drinking water for 1, 4, and 16 mo (13 treated rats per duration and 21 control rats per duration). Drinking water was fortified with five essential metals (1 ppm molybdenum, 1 ppm cobalt, 5 ppm copper, 10 ppm manganese, and 50 ppm zinc). All animals received a rye-based diet with low trace metal content based on that used by Schroeder and Mitchener (1975a,b). Based on a time-weighted average (TWA) water intake (20 mL/day) and body weight (0.334 kg) estimated from reported values for the 16-mo period, barium doses from drinking water can be estimated at 0, 0.060, 0.60, and 6.0 mg Ba/kg-day. The diet contained 1.5 ppm barium. Based on the TWA body weight and a TWA food intake of 20 g/day estimated from reported values for the 16-mo period, the barium dose from the diet can be estimated at 0.090 mg Ba/kg-day. Combining the doses from water and diet results in estimated intakes of 0.09, 0.15, 0.69, and 6.09 mg Ba/kg-day. The cumulative intake from drinking water and diet was reported by the authors as 16, 28, 134, and 1,198 mg Ba/rat for the 0, 1, 10, and 100 ppm groups at 16 mo (termination). Dividing the total doses by the TWA body weight and by 487 days (16 mo) gives estimated doses from water plus diet of 0.098, 0.17, 0.82, and 7.4 mg Ba/kg-day. These values are similar to those estimated above from the water and diet concentrations of barium. All the above estimates are approximate because the authors reported intake and body weight values only for controls, stating that the values for the dosed groups were no different. Accordingly, the TWA body weight and water and food intake values above were based on the control data and were used for all exposure groups.

Systolic blood pressures and body weights were measured at 1, 2, 4, 8, 12, and 16 mo, and organs (heart, liver, kidney, and aorta) were collected, weighed, and assayed for barium at 1, 4, and 16 mo. No change in mean systolic blood pressure was seen in groups exposed to 1 ppm barium in the drinking water. However, after 8 mo of exposure to 10 ppm, mean systolic blood pressure had increased by 6 mm Hg ($p < 0.01$) and continued to be significantly elevated through 16 mo (+4 mm Hg, $p < 0.01$). Significant increases ($p < 0.01$) in mean systolic blood pressure were evident at 100 ppm starting at 1 mo (+12 mm Hg) and continuing through 16 mo (+16 mm Hg) of exposure to 100 ppm barium in the drinking water. An additional 12 rats exposed for 16 mo to 100 ppm had a reduction of ATP and phosphocreatinine content of the myocardium, depressed rates of cardiac contraction, and depressed electrical excitability as compared with an additional control group of 18 rats. No mortalities were reported. Growth rates were unaffected by barium, as were tissue weights. A significant increase in barium levels was observed in the hearts of rats exposed to 100 ppm. No other changes in barium levels or organ weights were reported. This study identifies a NOAEL of 1 ppm (0.17 mg Ba/kg-day) and a LOAEL of 10 ppm (0.82 mg Ba/kg-day) for hypertension in rats maintained on low-mineral-content diets.

The differences in the cardiovascular outcome of the Perry et al. (1983, 1985, 1989) study as compared with the NTP (1994) and McCauley et al. (1985) studies may have been confounded

by differences in diet composition. Rats in the Perry et al. (1983, 1985, 1989) study were maintained on a rye-based diet that contained low levels of several elements compared with standard laboratory chow (e.g., Purina chow), including calcium (3,800 vs. 12,000 ppm) and potassium (7,600 vs. 8,200 ppm). Animals maintained on diets low in calcium and/or potassium may be more sensitive to the cardiovascular effects of barium. The calcium content of the above rye-based diet is below the minimum requirement according to the NRC (1995); the potassium content is not. Acute effects of barium on the cardiovascular system are modified by calcium and potassium. Barium has been shown to be a calcium agonist (Perry et al., 1989; Brenniman et al., 1981; Shanbaky et al., 1978; U.S. EPA, 1990; WHO, 1990). Potassium alleviates the cardiac effects and skeletal muscle effects associated with acute barium poisoning (Gould et al., 1973; Roza and Berman, 1971; Diengott et al., 1964; U.S. EPA, 1990; WHO, 1990). Perry and Erlanger (1982) observed that rats maintained on the rye-based diet and exposed to cadmium developed hypertension, whereas rats maintained on standard chow and exposed to cadmium did not. In view of a possible association between the barium-induced cardiovascular effects and calcium and potassium intake, the applicability of dose-response data from the Perry et al. (1983) study to RfD derivation is not considered appropriate.

Schroeder and Mitchener (1975a) exposed Long-Evans rats (52/sex/group) to 0 or 5 ppm barium (barium acetate) in drinking water from weaning to natural death. Dosages from drinking water were 0.61 mg Ba/kg-day for males and 0.67 mg Ba/kg-day for females based on reference body weights and water intakes from U.S. EPA (1988). The diet was characterized as a "low metal" diet, and it included 60% rye flour, 30% dried skim milk, 9% corn oil, 1% iodized chloride, and assorted vitamins; the barium content was not reported. Barium had no significant effect on the growth of males, but increased the growth of older females. The lifespan of the rats was not significantly affected. The incidence of proteinuria in males exposed to barium for approximately 152 days (at 173 days of age) was significantly ($p < 0.05$) higher than in controls; proteinuria was assessed by a dipstick method, and the magnitude was not reported. Female rats at 532 and 773 days of age had higher ($p < 0.001$) serum cholesterol concentrations than did controls tested at 516 and 769 days of age. Serum glucose levels for males at these ages were also different from controls but did not follow an age-related pattern. The authors attached no biological or toxicological significance to these serum chemistry results. Histopathology of heart, lung, kidney, liver, and spleen did not reveal alterations. No significant increases in the number of gross tumors were observed in the barium-exposed male (8/30) or female (15/33) rats as compared with the controls (4/26 and 17/24 for males and females, respectively). This study identifies a LOAEL of 0.61 mg Ba/kg-day for renal glomerular damage evidenced as proteinuria in male rats maintained on low-mineral diets.

Schroeder and Mitchener (1975b) exposed white mice of the Charles River CD strain (36-54/sex) to 0 or 5 ppm barium (as barium acetate) in drinking water for their lifetimes. Dosages from drinking water were 1.18 mg Ba/kg-day for males and 1.20 mg Ba/kg-day for females (U.S. EPA, 1988). The diet was characterized as a "low-metal" diet, and it included 60% rye flour, 30% dried skim milk, 9% corn oil, 1% iodized chloride, and assorted vitamins; the barium content of the diet was not reported. Growth and body weights were not affected by the barium treatment. Histology of the heart, lung, liver, kidney, and spleen was normal. In males, longevity (defined as the mean lifespan of the last surviving five animals of each sex in each treatment group) was significantly ($p \leq 0.025$) reduced; longevity of the barium-treated

males was 815 days as compared with 920 days for the controls. The mean lifespan, however, was not affected. The incidences of lymphoma leukemia and lung tumors in the male (7/37 and 4/37, respectively) and female (5/21 and 3/21, respectively) mice exposed to barium were not significantly different from the incidences in the control mice (3/38 and 3/47 for lymphoma leukemia in males and females, respectively, and 5/38 and 9/47 for lung tumors).

4.2.2. Inhalation Exposure

Data on the toxicity of barium compounds in animals following inhalation exposure is limited to a subchronic study conducted by Tarasenko et al. (1977). In this study, male albino rats (strain and number of animals per group were not reported) were exposed to 0, 1.15, or 5.20 mg/m^3 barium carbonate (0, 0.80, or 3.6 mg Ba/m^3) for 4 h/day, 6 days/week for 4 mo. No information on aerosol generation or the size distribution of the particles was reported. In the introduction section of the paper, the authors state, "We have demonstrated by electron microscopy that the size of almost 80% of the dust particles is less than 2 µm"; however, it is not known if this statement refers to the aerosols generated for this study. The following endpoints were used to assess toxicity: body weight gain, arterial pressure, hematological (hemoglobin, leukocytes, and thrombocytes) and serum chemistry (glucose, phosphorus, total protein, alkaline phosphatase, and cholinesterase) parameters, urine calcium levels, bromosulfophthalein test of liver function, electrocardiogram measurement, and histological examination (tissues examined were not listed).

The authors noted that no alterations were observed in the rats exposed to 1.15 mg/m^3 barium carbonate. In the 5.20 mg/m^3 group, a number of alterations were reported; however, it does not appear that the data were statistically analyzed. The alterations included a 21% decrease in body weight gain, a 32% increase in arterial pressure, altered hematological parameters (decreases in hemoglobin and thrombocyte levels and increases in leukocyte levels), altered serum chemistry parameters (decreased sugar and total protein levels, increased phosphorus levels, decreased alkaline phosphatase activity, and increased cholinesterase activity), increased calcium levels in the urine, impaired liver function, and histological alterations in the heart, liver, kidneys, and lungs. No alterations in the EKG readings were reported. However, when the rats were administered proserine, the EKG reading suggested disturbances in heart conductivity. The authors noted that the heart, liver, and kidneys "had a character of mild protein ('granular') dystrophy." In the lungs, the histological alterations consisted of moderate perivascular and peribronchial sclerosis with focal thickening of the intraalveolar septa and collagenation. No incidence data were provided.

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES—ORAL AND INHALATION

4.3.1. Oral Exposure

Data on the reproductive and developmental toxicity of barium compounds are limited. The oral database consists of single-generation reproductive toxicity studies in rats and mice (Dietz et al., 1992) and a developmental toxicity study conducted by Tarasenko et al. (1977).

The lack of information on the animal species, barium dosages, and mode of administration and the poor reporting of results preclude using the Tarasenko et al. (1977) study to assess developmental toxicity following oral exposure.

In the Dietz et al. (1992) study, groups of male and female F344/N rats and B6C3F1 mice (20/sex/species/group) were exposed to barium chloride dihydrate in the drinking water for 60 days (males) or 30 days (females). The barium chloride dihydrate concentrations were 0, 1,000, 2,000, or 4,000 ppm for the rats and 0, 500, 1,000, or 2,000 ppm for the mice. Dosages were not reported for this study. The dosages from the subchronic study (Dietz et al., 1992; NTP, 1994) were therefore used to represent approximate dosages for this study. For the rats, estimated dosages were 65, 110, and 200 mg Ba/kg-day for the treated male groups and 65, 115, and 180 mg Ba/kg-day for the treated female groups. For the mice, these dosages were estimated at 55, 100, and 205 mg Ba/kg-day for the treated male groups and 60, 110, and 200 mg Ba/kg-day for the treated female groups. After the exposure period, males and females from the same exposure groups were housed together until there was evidence of mating or until the end of the mating period (8 days). The following endpoints were used to assess potential reproductive toxicity: length of pregnancy; number of implantation sites; number of live and dead offspring; pup weights at birth and on the fifth day after parturition; external abnormalities of pups; gross examination of the vagina, cervix, oviduct, and uterus of the F_0; evaluation of sperm density, morphology, and motility; and male reproductive organ weights of the F_0.

The observed pregnancy rates in the rats were below generally accepted norms for reproduction studies. The pregnancy rates ranged from 40% in the controls to 65% in the 4,000 ppm group and did not appear to be adversely affected by barium exposure. No significant alterations in gestation length, pup survival, or the occurrence of external abnormalities were observed in the rats. Marginal reductions (not statistically significant) in the number of implants per pregnant dam and live litter size at birth and day 5 were observed in the 4,000 ppm group. A statistically significant ($p < 0.01$) decrease in live pup weight at birth was observed in the 4,000 ppm group (5.2 g vs. 5.7 g in controls); however, no significant alterations in pup body weight were observed at 5 days of age. Low pregnancy rates were also observed in the mice; the pregnancy rates ranged from 55% in controls to 55%-70% in the barium-exposed groups. No alterations in maternal weight gain, average length of gestation, pup survival, or pup weights were observed in the mice. A statistically significant ($p < 0.05$) decrease in average litter size occurred on days 0 and 5 at 1,000 ppm but not at 2,000 ppm. No external abnormalities were observed in the mice offspring. No alterations in epididymal sperm counts, sperm motility, sperm morphology, testicular or epididymal weights, or vaginal cytology were observed in the rats or mice. The results of this study suggest that oral exposure to barium chloride doses of $\leq$ 200 mg Ba/kg-day does not result in reproductive toxicity; however, the results should be interpreted cautiously because of the below-normal pregnancy rates in all groups of rats and mice.

4.3.2. Inhalation Exposure

Information on the reproductive/developmental toxicity of inhaled barium compounds is limited to a series of studies conducted by Tarasenko et al. (1977). The results of these studies

were described in general terms and no data were provided. The poor reporting of the study design and results and the lack of statistical analysis of the data limit the usefulness of the data for assessing the reproductive/developmental toxicity of barium.

Exposure of male rats to 22.6 mg/m^3 barium carbonate (15.7 mg Ba/m^3) for one cycle of spermatogenesis (daily exposure duration and frequency of exposure were not reported) resulted in decreases in the number of spermatozoids, decreased percentage of motile forms and time of motility, decreases in osmotic resistance of spermatozoids and increases in the number of ducts with desquamated epithelium, and a reduced number of ducts with 12th stage meiosis (Tarasenko et al., 1977). Similar results were observed in rats exposed to 5.2 mg/m^3 barium carbonate (3.6 mg Ba/m^3) 4 h/day, 6 days/week for 4 mo.

Tarasenko et al. (1977) also reported that a shortening of the mean duration of the estrous cycle and an alteration in the proportion of mature and dying ovarian follicles were observed in rats exposed to 13.4 mg/m^3 barium carbonate (9.3 mg Ba/m^3) for 4 mo (duration of daily exposure or frequency of exposure were not reported), as compared with a control group. These effects were not observed in rats exposed to 3.1 mg/m^3 (2.2 mg Ba/m^3). The authors also noted that rats in the 13.4 mg/m^3 group gave birth to underdeveloped offspring that showed considerable mortality and slow increases in body weight during the first 2 mo of life. The authors did not state whether the barium carbonate-exposed females were mated to exposed or unexposed males.

4.4. OTHER STUDIES

4.4.1. Acute Toxicity Data

Intentional or accidental ingestion of barium compounds causes gastroenteritis, hypokalemia, hypertension, cardiac arrhythmias, and skeletal muscle paralysis. Potassium infusion is used clinically to reverse many of the toxic effects, but it does not reverse the hypertension (Diengott et al., 1964; Gould et al., 1973; U.S. EPA, 1990; WHO, 1990).

Intravenous infusion of barium chloride into anesthetized dogs or guinea pigs resulted in increased blood pressure and cardiac arrhythmias (Hicks et al., 1986; Roza and Berman, 1971). The study in dogs also reported skeletal muscle flaccidity and paralysis (Roza and Berman, 1971). In the dog study, determination of plasma potassium concentrations revealed severe hypokalemia, which appeared to result from an extracellular-to-intracellular shift of potassium. The hypertension did not appear to be mediated through the renin-angiotensin system because it was not prevented by bilateral nephrectomy of the dogs. Simultaneous infusion of potassium into the dogs abolished the cardiac effects and the skeletal muscle flaccidity but did not affect hypertension.

4.4.2. Mechanistic Studies—Cardiovascular Toxicity

As mentioned during discussion of the cardiovascular studies of Perry et al. (1983, 1985, 1989), barium appears to act as a calcium agonist and interacts with potassium by increasing its active inward cellular transport and blocking its outward passive diffusion, which results in hypokalemia (U.S. EPA, 1990; WHO, 1990).

Although the data of Roza and Berman (1971) for bilaterally nephrectomized dogs indicate that the hypertensive effects of barium seen in acute poisoning are not mediated through the renin-angiotensin system, the possibility of such a mechanism during long-term, low-level exposure to barium does not appear to have been investigated. No direct information on the possible effects of barium on plasma renin levels or renin release was found. However, based on what is known about the effects of barium on cellular metabolism of calcium and potassium and on signal transduction pathways involved in the control of renin release (Ballerman et al., 1986), it would not be surprising if barium were to affect the release of renin. Renin is synthesized and released from granulated myoepithelial cells of the juxtaglomerular apparatus (JGA) in the kidney. Specialized secretory cells of the JGA synthesize and secrete renin in response to a variety of chemical and physical signals relating to extracellular fluid volume and blood pressure. Control of renin release is achieved through a balance between inhibitory and stimulatory signals to these secretory cells. In general, at the cellular level, inhibitory signals are processed through Ca^{2+}-calmodulin-dependent mechanisms and are sensitive to intracellular Ca^{2+} concentrations. An increase in intracellular Ca^{2+} inhibits renin release by promoting formation of Ca^{2+}-calmodulin complex.

It is conceivable that barium could affect renin release from the kidney by several different mechanisms. If barium were to produce vasoconstriction, one would expect a decrease in renin release in response to any resulting increase in blood pressure (Ballerman et al., 1986). If barium were to stimulate neurotransmitter release from renal nerve terminals, an increase in renin release would be expected (Ballerman et al., 1986). Barium has been shown to stimulate neurotransmitter release from in vitro preparations of isolated nerve terminals (Verhage et al., 1995). This effect appears to involve at least two distinct mechanisms: (1) barium-induced depolarization of the nerve terminal that results from blockade of K^+ channels, and (2) a direct action of barium on the Ca^{2+}-mediated signal transduction pathways that control neurotransmitter release.

It also is conceivable that barium could act directly on JGA secretory cells to stimulate renin release. Renin release is inhibited by depolarization of JGA secretory cells, which activates voltage-operated Ca^{2+} channels and results in an influx of extracellular Ca^{2+} into the cells (Ballerman et al., 1986). Barium could depolarize JGA secretory cells by blocking K^+ channels in these cells and, thereby, inhibiting renin release. If barium were to raise intracellular Ca^{2+} concentrations by stimulating the release of Ca^{2+} from intracellular stores (Verhage et al., 1995) or inhibiting transport of Ca^{2+} out of the cell via the Ca^{2+}-ATPase (WHO, 1990), either action would inhibit renin release. It also is conceivable that barium could inhibit renin release by a direct action on Ca^{2+}-mediated signal transduction pathways that control renin release, similar to effects of barium on neurotransmitter release in nerve terminals (Verhage et al., 1995). All of these mechanisms would tend to inhibit rather than promote the release of renin from the JGA

secretory cells. Thus, mechanistic considerations do not provide a clear answer regarding whether barium would stimulate or inhibit renin release.

4.4.3. Intratracheal Administration

In a study conducted by Tarasenko et al. (1977), animals (it appears that albino rats and rabbits were tested; number of animals not specified) were administered an intratracheal dose of 50 mg barium carbonate (35 mg barium). Three months after administration, sclerotic changes were observed in the lungs. The severity of the sclerosis progressed. At 9 mo, fibrous pneumonia with necrosis of mucous membrane of the large bronchi was also observed.

Uchiyama et al. (1995) administered a single intratracheal dose of 0.015, 0.3, or 0.6 mL/kg of Ba147 to rabbits. Ba147 is a preparation containing 85% barium sulfate. No treatment-related effects on pulmonary ventilation (measured 1 day, 3 days, and 1, 2, and 4 weeks after dosing), levels of blood gases (measured at the same time as pulmonary ventilation), or lung weights were observed. Soft x-rays of the lungs revealed dose-related shadows. Bronchopneumonia, bronchitis, or bronchiolitis was observed in 28 of 36 animals during the first week after dosing. Thereafter, the alterations were not observed. No further details of this study were available because the study was published in a Japanese-language journal; information on the study was obtained from an English abstract.

4.4.4. Carcinogenicity Studies—Topical Administration

In a study to determine the safety of components of intrauterine contraceptive devices, a single topical application of 1.25 mM barium chloride was applied to the squamocolumnar junctional area of the cervix of a woman with no known history of abnormal cervical cytology results (Ayre, 1966; Ayre and LeGuerrier, 1967). A cervical cell scraping was performed 48 h after barium chloride application. The topical application of barium chloride and cervical cell scraping were repeated four times at intervals of 4-6 weeks. A number of cell transformations resembling severe premalignant dysplasia were observed; the transformed cells were described as bizarre, multinucleated cells with profoundly altered nuclear chromatin. One to three weeks after barium chloride application, these cellular alterations were no longer observed.

In another study (Ayre, 1966; Ayre and LeGuerrier, 1967), 1.25 mM barium chloride was mixed with equal amounts of 70% DMSO, and a single topical application of the mixture was applied to the squamocolumnar junctional area of the cervix. It is assumed that only one subject was used, and it was not reported whether this was the same woman previously tested. Cervical scrapings were performed after 48 h, 72 h, and twice weekly for an unspecified amount of time. The cell transformations were similar to extreme dysplasia; in addition, spindle cells and cells with marked hyperchromatism with multiple chromatin bundles and enlarged irregular nucleated forms were observed. Cell transformations were also observed in deeper layers of the squamous epithelium. The authors noted that the transformed cells resembled cell findings of cancer in situ. Sixteen days after topical application, the cell transformations were not observed in the deeper layers of the epithelium but were still present in superficial and intermediate areas.

4.4.5. Genotoxicity

There is a limited amount of information available on the genotoxicity of barium compounds. No in vivo studies have been conducted. Most in vitro studies have found that barium chloride and barium nitrate did not induce gene mutations in bacterial assays with or without metabolic activation. Ames assays with *Salmonella typhimurium* strains TA1535, TA1538, TA1537, TA97, TA98, and TA100 with or without metabolic activation (Monaco et al., 1990, 1991; NTP, 1994), rec assays with *Bacillus subtilis* strains H17 and H45 (Nishioka, 1975; Kanematsu et al., 1980), and a microscreen assay with *Escherichia coli* (Rossman et al., 1991) with metabolic activation have produced negative results with barium chloride. Negative results have also been observed for barium nitrate in the rec assay using *B. subtilis* strains H17 and H45 (Kanematsu et al., 1980). Barium chloride induced gene mutations in L5178Y mouse lymphoma cells with metabolic activation but not in the absence of metabolic activation (NTP, 1994). Neither barium acetate nor barium chloride decreased the fidelity of DNA synthesis in avian myeloblastosis virus DNA polymerase (Sirover and Loeb, 1976). In mammalian cells, barium chloride did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, with or without activation (NTP, 1994).

4.5. SYNTHESIS AND EVALUATION OF MAJOR NONCANCER EFFECTS AND MODE OF ACTION—ORAL AND INHALATION

4.5.1. Oral Exposure

Barium causes cardiovascular effects, including hypertension and arrhythmias, in humans and animals when ingested acutely in high doses or administered parenterally. In addition, skeletal muscle paralysis and hypokalemia occur. The cardiac and skeletal muscle effects can be reversed by administration of potassium and thus are thought to be mediated by the antagonism of barium to potassium. Barium blocks potassium efflux from cells and stimulates the active inward transport of potassium (U.S. EPA, 1990; WHO, 1990). Barium also substitutes for calcium in some cellular processes involved in signal transduction and, through blockage of potassium efflux, may allow for greater calcium influx into the cell. The hypertensive action of barium, however, is not reversed by infusion of potassium. In addition, limited data indicate that the acute hypertensive effects of barium are not mediated through release of pressor substances, because removal of the kidneys or adrenals prior to barium administration does not prevent hypertension. Accordingly, it has been hypothesized that barium results in hypertension by stimulating the arteriolar smooth muscle directly (Roza and Berman, 1971; U.S. EPA, 1990).

Additional evidence for the hypertensive effects of barium has been obtained in subchronic and chronic drinking water studies of barium toxicity in rats given diets low in trace minerals, calcium, and potassium (Perry et al., 1983, 1985, 1989). Subchronic studies in which rodents were administered barium in drinking water and fed adequate diets indicated that renal effects, including glomerular effects, were a more sensitive endpoint of barium toxicity in rats than was hypertension (NTP, 1994; McCauley et al., 1985). However, a similar relationship may not occur following chronic exposure or in humans. A subchronic experimental study in humans

(Wones et al., 1990) and a well-designed morbidity study of residents receiving high or low levels of barium in their drinking water establish a NOAEL of 0.21 mg Ba/kg-day for hypertension. This NOAEL may apply to renal disease as well, but this condition was assessed only by asking the participants whether they had physician-diagnosed renal disease. A LOAEL was not identified in these human studies.

4.5.2. Inhalation Exposure

Several human studies have investigated the toxicity of inhaled barium compounds. Exposure to insoluble forms of barium such as barium sulfate and barite ore results in baritosis (Pendergrass and Greening, 1953; Seaton et al., 1986; Doig, 1976). Although profuse opacities are observed on the radiographs, no alterations in lung function, abnormal physical findings, or increases in the incidence of subjective symptoms have been reported. It appears that the accumulation of barium sulfate in the lungs will diminish upon termination of barium exposure. Barium exposure levels resulting in baritosis have not been reported. NIOSH (1982) reported an increased incidence of hypertension in workers exposed to an unspecified concentration of barium. Although the results of this study are consistent with the suggestion of hypertension following oral exposure to barium compounds, the results of the NIOSH (1982) study should be interpreted cautiously because it is likely that the workers were also exposed to other metals, including lead, which has a known hypertensive effect.

Inhalation toxicity data in animals are limited to inhalation exposure and intratracheal administration studies by Tarasenko et al. (1977) and an intratracheal administration study by Uchiyama et al. (1995). In the Tarasenko et al. (1977) inhalation study, a number of adverse effects were reported in rats exposed to 5.20 mg/m^3 barium carbonate (3.6 mg/m^3 barium) 4 h/day, 6 days/week for 4 mo. The effects included alterations in some hematological and serum chemistry parameters, perivascular and peribronchial sclerosis with collagenation in the lungs, and increases in arterial pressure. It does not appear that statistical analysis of the data was performed, and incidence data for the lung effects were not reported. No adverse effects were observed in the rats exposed to 1.15 mg/m^3 barium carbonate (0.80 mg/m^3 barium). The finding of lung lesions following exposure to barium carbonate was confirmed by an intratracheal administration study conducted by Tarasenko et al. (1977). In this study, fibrous pneumonia and necrosis of the mucous membrane of the large bronchi was observed 9 mo after animals received an intratracheal dose of 50 mg barium carbonate (35 mg barium). As with the inhalation study, the results of this study were poorly reported. Uchiyama et al. (1995) also found pulmonary effects (bronchopneumonia, bronchitis, or bronchiolitis) in rabbits intratracheally administered a suspension containing 85% barium sulfate. Although studies conducted by Tarasenko et al. (1977) suggest that inhalation exposure to barium carbonate may result in reproductive effects, confidence in these studies is very low due to poor reporting of study design and results. Thus, the potential of barium to induce developmental and/or reproductive effects has not been adequately assessed following inhalation exposure.

4.6. WEIGHT-OF-EVIDENCE EVALUATION AND CANCER CHARACTERIZATION—SYNTHESIS OF HUMAN, ANIMAL, AND OTHER SUPPORTING EVIDENCE, CONCLUSIONS ABOUT HUMAN CARCINOGENICITY AND LIKELY MODE OF ACTION

In the only available human study, cell transformations were observed following a single topical application of barium chloride to the cervix (Ayre, 1966; Ayre and LeGuerrier, 1967). These transformed cells were exfoliated, and no alterations were observed 3 weeks after application.

Oral exposure studies in rats and mice (NTP, 1994; McCauley et al., 1985; Schroeder and Mitchener, 1975a,b) did not find significant increases in tumor incidence following chronic exposure. The design of the McCauley et al. (1985) and Schroeder and Mitchener (1975a,b) studies was inadequate for carcinogenicity evaluation. In the McCauley et al. (1985) study, small numbers of animals of one sex were exposed to relatively low concentrations of barium chloride for less than a lifetime. The absence of adverse effects suggests that the maximum tolerated dose (MTD) may not have been achieved in this study. In the Schroeder and Mitchener (1975a) rat study, only the incidence of total gross tumors was reported; the lack of adverse effects suggests that the only dose used was lower than the MTD. The decrease in longevity in the mouse study by Schroeder and Mitchener (1975b) suggests that the MTD may have been achieved in this study. However, it appears that only two types of cancer were examined (leukemia and lung tumors).

The design of the rat and mouse NTP (1994) studies was adequate to assess carcinogenicity. These studies used an adequate number of animals per group, exposed animals for 2 years, tested several dosage levels, and examined an extensive number of tissues. The decreased survival and histological alterations in the kidneys of the mice and the increased kidney weights in the rats suggest that the MTD was achieved in both of these studies. No carcinogenic effects were observed in either species. In fact, significant negative trends in the incidence of leukemia, adrenal tumors, and mammary gland tumors were observed in the rats.

The inhalation exposure and intratracheal studies conducted by Tarasenko et al. (1977) are inadequate for carcinogenicity evaluation because of several deficiencies in the design and reporting, including single or subchronic exposure duration, inadequate reporting of aerosol generation methodology, inferior reporting of study results (including the apparent lack of statistical analysis), and the use of only one sex (males). These studies were designed to be toxicity studies, and it is not known if the investigators looked for tumors.

Under EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986), barium would be classified as Group D, not classifiable as to human carcinogenicity. Although adequate chronic oral exposure studies in rats and mice have not demonstrated carcinogenic effects, the

lack of adequate inhalation studies precludes assessing the carcinogenic potential of inhaled barium.

Under the Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a), barium is considered not likely to be carcinogenic to humans following oral exposure, and its carcinogenic potential cannot be determined following inhalation exposure.

4.7. SUSCEPTIBLE POPULATIONS

4.7.1. Possible Childhood Susceptibility

Limited data exist on which to make an assessment of possible childhood susceptibility. Gastrointestinal absorption data suggest that barium absorption may be higher in children than in adults. Studies in rats (Taylor et al., 1962) and dogs (Cuddihy and Griffith, 1972) suggest that absorption in the younger animals is approximately tenfold higher than absorption in the older animals. The mechanism behind this apparent increased absorption efficiency in younger animals is not known, and it is not known if similar findings would be observed in humans. There are no human data examining age-related differences in susceptibility to barium toxicity.

4.7.2. Possible Gender Differences

The extent to which men differ from women in susceptibility to barium is not known. No gender differences were observed in human studies. However, one of the critical effects of barium following oral exposure is hypertension, and men are the presumptive sensitive population for hypertension. In the NTP (1994) subchronic and chronic rat studies, females appeared to be more sensitive than the males to the barium-induced increases in kidney weight. No other significant gender differences have been observed in animal studies.

5. DOSE-RESPONSE ASSESSMENTS

5.1. ORAL REFERENCE DOSE (RfD)

5.1.1. Choice of Principal Study and Critical Effect—With Rationale and Justification

No single study is appropriate as the basis for a lifetime RfD for barium. The RfD is based on a weight-of-evidence approach that focuses on four coprincipal studies: the Wones et al. (1990) experimental study in humans, the Brenniman and Levy (1984) epidemiologic study, and the subchronic and chronic rat studies that employed adequate diets and investigated both cardiovascular and renal endpoints (NTP, 1994). The McCauley et al. (1985) study of unilaterally nephrectomized rats was used to support the identification of the kidney as a co-critical target. In addition, the approach includes a consideration of supporting information from acute and mechanistic studies as well as from subchronic to chronic studies of animals on low-mineral diets.

The identification of hypertension as a health endpoint of concern is supported by findings of hypertensive effects in humans who ingested acutely high doses of barium compounds, in workers who inhaled dusts of barium ores and barium carbonate, in experimental animals given barium intravenously, and in rats exposed to barium in drinking water while on restricted diets. Based on these findings, lower dose human studies were conducted to examine the potential effects on blood pressure in humans, and both blood pressure and kidney function in animals. Although the experimental study by Wones et al. (1990) together with the epidemiological study by Brenniman and Levy (1984) did not report any significant effects on blood pressure, they establish a NOAEL in humans of 0.21 mg Ba/kg-day. The animal data suggest that the kidney may also be a sensitive target for ingested barium from low level exposure (McCauley et al., 1985; NTP, 1984; Schroeder and Mitchener, 1975a); neither of the human studies investigated sensitive renal endpoints. Therefore, 0.21 mg Ba/kg-day is used as the basis to derive the RfD. The use of a NOAEL from human studies increases the confidence in the Agency's judgement in the derivation of the RfD, which is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a life time.

5.1.2. Methods of Analysis—NOAEL/LOAEL

A NOAEL/LOAEL approach was used to derive the RfD for barium. The RfD was based on the no-effect levels identified in the Wones et al. (1990) and Brenniman and Levy (1984) human studies. The lack of adverse effect levels in the human studies precluded deriving an RfD using a benchmark concentration analysis approach.

5.1.3. RfD Derivation, Including Application of Uncertainty Factors (UF) and Modifying Factors (MF)

An uncertainty factor of 3 accounts for some database deficiencies and potential differences between adults and children. The RfD for barium is based on four principal studies. Two human studies (Brenniman and Levy, 1984; Wones et al., 1990) identified no human health effects in adults. Two well-designed rat studies (NTP, 1994) identified NOAELs and LOAELs for renal effects following subchronic or chronic exposure. The results of the NTP (1994) subchronic study suggest that under these test conditions renal effects may be a sensitive endpoint. However, a similar relationship may not occur following chronic exposure or in humans. Perry et al., 1983, 1985, 1989 reported that a marginally adequate diet, particularly one with inadequate calcium levels, may increase sensitivity to barium-induced hypertension. The Brenniman and Levy (1984) study examined more than 2,000 men and women; it is very likely that a wide range of dietary variability, including low calcium intakes, was represented in this population. Additionally, it is likely that this population included individuals unusually susceptible to the toxicity of barium. Dog and rat pharmacokinetic studies (Taylor et al., 1962; Cuddihy and Griffith, 1972) suggest that gastrointestinal absorption of barium may be higher in young animals than in older animals. Brenniman and Levy (1984) examined persons 18-75+ years of age living in the community for more than 10 years. It is likely that this study included adult residents who were exposed to elevated barium levels as young children, but it may not account for all of the uncertainty. The barium database consists of subchronic and chronic toxicity studies in three species (humans, rats, mice) and a marginally adequate first-generation reproductive / developmental toxicity study. This rat and mouse study (Dietz et al., 1992) gave no indication that developmental or reproductive endpoints are more sensitive than other endpoints; interpretation of the study results is limited by very low pregnancy rates in all groups, including controls, and examination of a small number of developmental endpoints.

No modifying factor is proposed for this assessment.

The RfD for barium is as follows: RfD = 0.21 mg/kg-day ÷ 3 = 0.07 mg/kg-day (or 7E-2 mg/kg-day).

5.2. INHALATION REFERENCE CONCENTRATION

The human (Pendergrass and Greening, 1953; Seaton et al., 1986; Doig, 1976) and animal inhalation (Tarasenko et al., 1977) and intratracheal (Tarasenko et al., 1977; Uchiyama et al., 1995) studies suggest that the respiratory system is a target of barium toxicity. The data also suggest that systemic effects, such as hypertension, may occur following inhalation exposure (NIOSH, 1982; Zschiesche et al., 1992; Tarasenko et al., 1977). The human studies cannot be used to derive an RfC for barium because exposure concentrations were not reported. Although the NIOSH (1982) study measured barium breathing zone levels for some groups of workers, the barium exposure levels were not measured in the group of workers with the increased incidence

of hypertension. The deficient reporting of the methods and results (in particular, the lack of information on the aerosol generation, number of animals tested, incidence data, and statistical analysis) of the only animal subchronic/chronic inhalation study (Tarasenko et al., 1977) preclude deriving an RfC for barium from the animal data.

5.3. CANCER ASSESSMENT

The oral database suggests that barium is unlikely to be carcinogenic to humans, and the inhalation database is inadequate to assess carcinogenicity. Thus, derivation of slope factors and unit risk values is precluded.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE-RESPONSE

6.1. HAZARD IDENTIFICATION

Barium is a dense alkaline earth metal that is widely distributed in small amounts in the earth's crust. Under natural conditions, barium occurs as the divalent cation in combination with other elements. Barium enters the environment through the weathering of rocks and minerals and through anthropogenic releases.

Longer term human studies (Brenniman and Levy, 1984; Wones et al., 1990) have found no adverse effects following oral exposure to lower concentrations of barium in drinking water. Hypertension has been observed in humans who ingested high doses of barium compounds under occupational exposure conditions.

Subchronic and chronic oral studies (NTP, 1994; McCauley et al., 1985) provide evidence that the kidney, including glomerular damage, is a sensitive target of barium toxicity in rats and mice fed a nutritionally adequate diet. Hypertension has been observed in studies (Perry et al., 1983, 1985, 1989) in which rats were fed a marginally adequate diet, particularly one with inadequate calcium levels.

Several case reports (Pendergrass and Greening, 1953; Seaton et al., 1986) and a prospective study conducted by Doig (1976) have reported baritosis in workers exposed to airborne barite ore or barium sulfate. Baritosis is considered a benign pneumoconiosis characterized by intense radiopacity of discrete opacities usually profusely disseminated throughout the lung. Spirometric lung function tests were normal in the workers examined by Doig (1976). Upon exposure termination, there is an apparent decrease in barium levels in the lung (Doig, 1976); the barium-related lesions are also potentially reversible (ACGIH, 1992). NIOSH (1982) reported an increased incidence of hypertension in workers exposed to an

unspecified concentration of barium; these results should be interpreted cautiously because it is likely that the workers were also exposed to other metals, including lead, which has a known hypertensive effect.

Data on the toxicity of inhaled barium to animals are limited. Tarasenko et al. (1977) reported perivascular and peribronchial sclerosis with collagenation in the lungs and increases in arterial pressure in rats exposed to barium carbonate. The deficient reporting of the methods and results (in particular, the lack of information on the aerosol generation, number of animals tested, incidence data, and statistical analysis) limits the usefulness of this study for hazard assessment.

A reproductive/developmental toxicity study did not find any significant alterations in gestation length, pup survival, or occurrence of external abnormalities in rats and mice exposed to barium chloride in drinking water (Dietz et al., 1992). The study also did not find any significant alterations in reproductive endpoints in the F_0 rats and mice. The low pregnancy rates in all groups, including controls, limit the usefulness of this study.

An area of scientific uncertainty concerning the noncancer hazard assessment for barium is identification of the most sensitive endpoint of barium toxicity in humans. The results of the NTP (1994) subchronic rat study suggest that renal effects may be a more sensitive endpoint than hypertension. However, it is not known if a similar relationship would exist following chronic exposure or in humans. The Brenniman and Levy (1984) human study examined the effect of barium on blood pressure but did not investigate sensitive renal endpoints (kidney disease was only assessed by a health questionnaire)**.** The chronic rat study (NTP, 1994) did not measure blood pressure. Another area of scientific uncertainty is whether any toxicological or toxicokinetic differences exist between children and adults. Animal data (Taylor et al., 1962; Cuddihy and Griffith, 1972) suggests that gastrointestinal absorption may be higher in children than in adults.

No oral human carcinogenicity data are available. Oral exposure studies in rats and mice (NTP, 1994; McCauley et al., 1985; Schroeder and Mitchener, 1975a,b) did not find significant increases in tumor incidence following chronic exposure to barium.

No inhalation carcinogenicity data are available for humans. The inhalation and intratracheal studies in animals conducted by Tarasenko et al. (1977) are inadequate for carcinogenicity evaluation because of several deficiencies in the design and reporting, including single or subchronic exposure duration, inadequate reporting of aerosol generation methodology, deficient reporting of study results (including the apparent lack of statistical analysis), and the use of only one sex (males).

Based on the weight of evidence, barium can be classified as Group D, not classifiable as to human carcinogenicity, using the 1986 guidelines (U.S. EPA, 1986). Although adequate chronic oral exposure studies in rats and mice have not demonstrated carcinogenic effects, the lack of adequate inhalation studies precludes assessing the carcinogenic potential of inhaled

barium. According to the proposed guidelines, barium would be considered not likely to be carcinogenic to humans following oral exposure, and its carcinogenic potential cannot be determined following inhalation.

The lack of adequate inhalation carcinogenicity data is an area of scientific uncertainty for this assessment.

6.2. DOSE-RESPONSE ASSESSMENT

A quantitative estimate of human risk as a result of low-level chronic barium oral exposure is based on weighing human and animal experiments; possible renal effects appear to identify the kidney as the most sensitive tissue. The human chronic dose of ingested barium considered to be without deleterious noncancer effect (the RfD) is 7E-2 mg/kg-day. This value is based on no effects identified in two human studies (0.21 mg/kg-day), and for kidney effects identified in subchronic (65 mg/kg-day) and chronic (45 mg/kg-day) rat studies. The RfD was calculated by dividing the NOAEL from the human study by an uncertainty factor of 3.

An uncertainty factor of 3 accounts for some database deficiencies and potential differences between adults and children. Because the Brenniman and Levy (1984) co-principal study examined more than 2,000 men and women, it is probable that this population included individuals unusually susceptible to barium. Although the Brenniman and Levy (1984) study did not examine children, the study did include persons 18-75+ years of age who lived in the community for more than 10 years. Thus, adult residents exposed to elevated barium levels as young children were likely included in the study population. This study may not account for all of the uncertainty regarding potential toxicological and/or toxicokinetic differences between children and adults. As discussed in the Toxicological Review, Chapter 4.2, the toxicity of barium has been examined in several subchronic and chronic studies of humans, rats, and mice and a marginally adequate reproductive/developmental toxicity study of rats and mice.

The overall confidence in this RfD assessment is medium. There is medium confidence in the human coprincipal studies because kidney effects have been identified in animal studies but not fully investigated in humans. The lack of cardiovascular measurements (heart rate, blood pressure, or electrocardiogram recordings) in the chronic animal studies that used adequate diets (NTP, 1994) reduces the confidence in the animal coprincipal studies. Confidence in the database is medium because of the existence of subchronic and chronic human studies, subchronic and chronic animal studies in more than one species, and a reproductive/developmental study in rats and mice. Medium confidence in the RfD reflects the medium confidence in the principal studies and the medium confidence in the database.

The RfD has been calculated from doses derived from human studies which show no adverse effects. If one were to solely depend upon data from animal studies demonstrating renal effects as the critical determinants for RfD calculation, the employment of customary uncertainty

factors would produce a RfD similar to that produced through the evaluation of data from human studies. However, the RfD derived using data from animal studies would include more uncertainty than the RfD derived using data from human studies. Direct human studies of good quality generally reduces the uncertainties and increases confidence in RfDs.

At the present time, no adequate data are available to derive an RfC for barium. The available human and animal data suggest that the respiratory tract may be a sensitive target of toxicity; thus, it would not be appropriate to derive an RfC for barium based on oral data.

Dose-response assessment for carcinogenic effects is not applicable because the oral data suggest that barium is not likely to be carcinogenic and the inhalation data are inadequate.

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8. APPENDICES

APPENDIX A: SUMMARY OF AND RESPONSE TO EXTERNAL PEER REVIEW COMMENTS

The Toxicological Review for Barium and all individual barium assessments have undergone both internal peer review performed by scientists within EPA or other Federal agencies and a more formal external peer review performed by scientists chosen by EPA in accordance with U.S. EPA (1994). The three external peer reviewers (see Contributors and Reviewers) submitted written comments on the overall assessment. A summary of comments made by the external reviewers and EPA's response to these comments follow.

The external peer reviewers offered editorial comments and many minor, but valuable, suggestions; these have been incorporated into the text to the extent feasible. Substantive scientific comments are addressed below. Several reviewers provided citations of papers they would like to see added to the Toxicological Review; studies that supported the hazard identification and dose-response assessments have been incorporated into the document.

Comment: One reviewer felt that the potential for children to be a high-risk population was generally ignored.

> ***Response to Comment:*** As discussed in Section 4.7.1 of the document, there are limited data with which to assess whether children are likely to be a sensitive subpopulation. The available data suggest that there are potential toxicokinetic differences between adults and young children; however, there are no data to assess potential age-related toxicity differences.

Comment: One reviewer suggested increasing the uncertainty factor for the RfD from 3 to 10. He felt that the increased uncertainty factor was justified to protect against potential effects in children and uncertainty as to the role of dietary variability. The other two external peer reviewers felt that the uncertainty factor of 3 was appropriate.

> ***Response to Comments***: EPA concludes that the uncertainty factor of 3 should be retained. The uncertainty factor of 3 was used to account for some database deficiencies and a potential difference between adults and children. It is likely that a wide range of dietary variability, including low calcium intakes, was represented in the Brenniman and Levy (1984) study population of more than 2,000 adults. The residents, aged 18-75+ years, examined in this study lived in the community for more than 10 years; thus, it is probable that the study included individuals who were exposed to elevated barium levels as children. However, this study may not account for all of the uncertainty that there may be differences between children and adults. The Agency feels that the current RfD would be protective for children.

Comment: One reviewer was uncomfortable with the apparent dismissal of the increased calcium levels observed in the Wones et al. (1990) human experimental study.

> ***Response to Comment:*** EPA feels that the slight increase in albumin-corrected serum calcium levels is not clinically significant. The adjusted serum calcium levels were 8.86, 9.03, and 9.01 mg/dL when the subjects were exposed to 0, 5, or 10 ppm barium, respectively. The Agency feels that this small change in calcium levels is not likely to result in adverse effects. In addition, studies in animals have shown no changes in serum calcium levels following short-term or chronic exposure to barium in drinking water (NTP, 1994; Tardiff et al., 1980). The Wones et al. (1990) study description in the document and RfD summary sheet was revised to include the serum calcium levels (adjusted and unadjusted levels were reported) and a note that the adjusted method used by Wones et al. (1990) is considered unreliable.

Comment: One reviewer expressed concern that the apparent barium-related increased mortality observed in the mortality portion of the Brenniman and Levy (1984) study was discounted.

> ***Response to Comment:*** EPA feels that it is not possible to assign a causal relationship between mortality and exposure to barium based on the results of this study because a number of potentially confounding variables were not controlled.

Comment: One reviewer noted that the finding of impaired lung function in > 20% of the workers examined by Doig (1976) is not an inconsequential finding.

> ***Response to Comment***: Five workers underwent lung function tests in 1963 (exposure was terminated in 1964). For three of the workers, the results were similar to predicted values (89%-119% of predicted values). Lung function tests were below predicted values (70%-85%) in the other two workers. The study authors noted that the impaired lung function was not likely due to barium exposure (one worker was an alcoholic and heavy smoker and the second worker had a fibrotic lung resulting from an early childhood illness). The Toxicological Review was revised to include lung function performance results and possible cause of the impaired lung function in the two workers.

Comment: One reviewer felt the discussion of why the data were inadequate for derivation of an RfC should be expanded, and the reviewer noted that the NIOSH (1982) study did report some breathing zone air barium levels.

> ***Response to Comment***: EPA feels that the inhalation database limitations are adequately discussed. The text was revised to note that although the NIOSH (1982) study measured barium breathing zone levels for some groups of workers, the barium exposure levels were not measured in the group of workers with the increased incidence of hypertension.

REFERENCES FOR APPENDIX A

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